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Section of Tropical Diseases and Parasitology.

President.—Dr. J. GORDON THOMSON.

[*May 5*, 1932.]

A Study of Induced Malignant Tertian Malaria.

By S. P. JAMES, W. D. NICOL and P. G. SHUTE.

SYNOPSIS.

(I) *Introduction.*—Justification for employing *P. falciparum* in the practice of malaria-therapy.

(II) *Origin of the strains of P. falciparum used.*—Eight strains of the parasite were used, of which two were from India, three from Rome, one from Sardinia and two from West Africa. The manner in which the strains were obtained is described and a list of cases infected with them, some by blood inoculation, others by the bites of mosquitoes, is given.

(III) *Problems of morphology and of biological properties.*—Two problems are discussed, namely: (1) Is there more than one species of malignant (crescent-forming) parasite? (2) Within the same species of malignant parasite are there various geographical races which, while not being morphologically different, can be recognized as being distinct by their clinical virulence, immunological reactions and other biological properties? The discussion of the latter problem includes a brief account of two cases of blackwater fever and one of the "pre-blackwater state" which occurred during the course of the inquiry.

(IV) *The temperature curve in malignant malaria.*—The different types of fever observed are described and illustrated, and an explanation of "the Marchiafava and Bignami curve" based on an analysis of them is given. The question is discussed whether or not there is a malignant parasite which completes its asexual cycle in twenty-four hours and therefore produces what is called malignant quotidian fever.

(V) *The general course of the disease in malignant malaria.*—The usual sequence of events following recovery from primary attacks of the malignant tertian disease is described, and it is explained how in this respect and in others malignant tertian malaria differs from benign tertian. There is a record of twenty-five cases which were under continuous observation for more than a year after the primary attack, and in an appendix charts are given to illustrate the general course of the disease throughout the whole of a particular infection. The bearing of these observations on treatment is pointed out. The general course of the parasitic infestation is also described and examples of persistence of parasites without fever are given.

(VI) *Treatment.*—(1) Various factors which influence the therapeutic effect of quinine and other antimalarial remedies are named and discussed, and it is pointed out that chemotherapeutic tests which do not take them into account are of little or no value. Two factors are of outstanding importance, namely (i) as regards the patient, the degree of natural or acquired "tolerance" or "immunity" to the infection which he possesses; (ii) as regards the parasite, the clinical virulence of the particular strain which caused the infection. The discussion as a whole leads to the view that the usual clinical practice of administering quinine in malignant tertian malaria as soon as the diagnosis has been made may not always be in the best interests of the patient. It is suggested that, when full information of all the circumstances and conditions of the case can be obtained, the scheme of treatment should be arranged as far as possible with a view to permit the patient to acquire an immunity against recrudescences of the disease. Attention is drawn to a possible risk of blackwater fever when one employs systems of continuous "after-treatment" with quinine to protect against relapses.

(2) The results of a test inquiry into the therapeutic efficacy in malignant tertian malaria of the new synthetic antimalarial preparation *atebrin* are described in some detail. The trials were made in a manner which eliminated usual causes of error in clinical chemotherapeutic tests. The conclusion is reached that the curative effect of this new synthetic preparation is very remarkable. Its discovery marks a new epoch in the therapeutics of malignant tertian malaria.

(I) Introduction.

It is a general rule in malariatherapy to induce the attack of malaria by means of the benign tertian parasite, *P. vivax*, or the quartan parasite, *P. malariae*. Several workers, having in mind the hypothesis that a more effective agent might be a species of parasite which sporulates in the capillaries of the brain and of other internal organs, have attempted to use the malignant tertian parasite, *P. falciparum*, but have found that the risks attending an attack of induced malignant malaria are usually so great as to prohibit a sufficient trial of the practice. At Horton, however, specialist experience in the care and management of cases of malaria is assisted by organized arrangements for expert laboratory control and trained nursing, so that at this hospital effective safeguards can be provided against those risks. In these circumstances we decided in August, 1927, that a tentative trial of malariatherapy with *P. falciparum* could be justified, particularly for the treatment of patients who had not benefited greatly from a course induced by one or other of the "benign" parasites. No untoward events followed infection of the first series of patients and, with increasing experience of the manner in which impending risks can be prevented, we gradually extended the trial to include patients who were not previously infected with any form of malaria. Among our first twenty-two cases there were three fatalities during, or shortly after, the malarial course, but in one of the cases the fatal issue was caused by advanced carcinoma not detected during life. Since then we have treated more than fifty cases without a death, so that the fatality-rate properly attributable to a malaria course with *P. falciparum* at Horton is only 4%, which is less than half the fatality-rate (10 to 14%) attributable to malaria courses with the benign tertian parasite, *P. vivax*, in mental hospitals in England and Wales [1]. For this reason we have no doubt that in particular circumstances the use of *P. falciparum* is justifiable and enables an effective course of malariatherapy to be given to some patients who would otherwise be deprived of this curative measure. The effects of the course on general paralysis will be described elsewhere by one of us (W. D. N.), so the present paper will be limited to observations relating to malaria.

(II) Origin of the Strains used.

The following statement indicates the strains of *P. falciparum* which were used for infecting our first fifty-four patients, the mode of their infection and their previous malarial history:—

Strain of parasite and date it was obtained	Patients infected by blood inoculation	Patients infected by mosquito bites	Patients who had been given a previous malaria therapeutic course	Patients with no malaria previously
Indian I (12.8.27)	3	0	2	1
Indian II (2.10.29)	16	0	10	6
Rome I (27.10.30)	3	2	3	2
Sardinia (27.10.30)	5	4	6	3
West Africa I (27.5.31) (Freetown) ...	1	1	2	0
Rome II (10.10.31)	3	13	8	8
Rome III (2.12.31)	0	1	1	0
West Africa II (14.1.32) (Lagos) ...	0	2	1	1
	31	23	33	21

Both the Indian strains were obtained by collecting blood from cases at the Seamen's Hospital, Albert Docks. The Rome I strain was obtained by one of us (P. G. S.) on the occasion of a study tour in Italy when a large number of our English *A. maculipennis* were taken to Rome and fed upon crescent cases which Professor Missiroli had selected for the purpose. The insects, after feeding, were incubated in Rome until developing oöcysts were found, and the rest of the batch was then brought back to Horton where our routine procedure of feeding and incubation was continued until sporozoites were found to be present in the salivary glands. Two

patients who had been selected for infection by this strain were bitten by infected insects on 27.10.31 and developed typical attacks. The strain was afterwards passed to other patients by blood inoculation. The Sardinia strain was obtained during the same visit by collecting all the adult anopheles (*maculipennis*) which could be found in malarious houses in the village of Posada. Some of these insects were brought back alive to Horton where a patient (Case 22) on whom they were fed developed an attack of malignant tertian malaria twelve days after being bitten. The strain was then passed by blood inoculation to two other patients (Cases 23 and 24), from one of whom we were able to infect a batch of English *maculipennis* which was used for infecting six cases. The strain, West Africa I, was brought to us by Dr. Barber (of the Rockefeller Foundation) in live specimens of *A. gambiæ* which he had infected at Freetown before starting on his voyage to England. He kept the insects alive during the voyage by allowing them to feed on himself before sporozoites were present in the glands and afterwards by allowing them to feed on raisins. The strains Rome II and Rome III were obtained from infected Italian *maculipennis* which Professor Missiroli fed on crescent cases in Rome and forwarded to us by air mail. The usual procedure of feeding and incubating the mosquitoes which survived the journey was continued at Horton and, when sporozoites were present in the glands, patients were infected by their bites. Only one mosquito of the Rome II batch survived long enough to infect the selected patient (Case 35), but from that patient the strain was passed by blood inoculation to Case 37, and from this case we succeeded in infecting a batch of English *maculipennis* which was used for infecting ten other patients. The West Africa II strain, like the West Africa I strain, was brought to us in *A. gambiæ*, but in this case the mosquitoes were reared from larvæ and fed on crescent carriers at Lagos by Mr. J. Y. Brown, European Sanitary Inspector, Public Health Department, Nigeria, who had worked with Dr. Barber in Liberia and had undertaken to help us by bringing home infected mosquitoes in the same way as Dr. Barber had done. Mr. Brown infected the batch in December and, as his departure for England was delayed, sporozoites were already present in the glands before his ship left Lagos. Nevertheless, on finding during the voyage that the daily mortality of the insects was such that without a feed of blood none could reach England alive, he decided to feed them upon himself and at the same time to test the efficacy of plasmoquine as a prophylactic. He took a dose of 0·06 gramme of the drug daily during the several days on which he gave the mosquitoes an opportunity of biting his forearm and the same dose daily for eight days after the last occasion on which he was bitten. Six insects were alive on arrival at Horton and all of them had had a full meal of his blood. They were at once applied to the patient who had been selected for infection with this strain, but none bit. They were therefore killed and dissected. All were found to have sporozoites in the glands, which proves that Mr. Brown must have received a heavy infection. The sporozoites from the salivary glands of one insect were injected intravenously in two selected cases. Both these patients (Cases 48 and 49) developed malignant tertian malaria within the usual incubation period, but Mr. Brown remained in his usual good health and has so continued to the present time, which is more than three months after the last occasion on which he was bitten.

(III) Problems of Morphology and of Biological Properties.

In any study of malignant malaria two problems are of outstanding interest. The first is whether there is more than one species of malignant (crescent-forming) parasite. This is exclusively a morphological problem. The second is exemplified by the common observation that in some parts of the world malignant malaria is more malignant than in others. Ziemann, for instance, writes: "In Upper Italy I saw cases of malignant malaria (perniciosa) which clinically seemed no more dangerous than ordinary benign tertian, while the same parasites on the coast of Tuscany produced

the most dangerous and violent symptoms" [2]. This is a problem relating to biological properties.

We think that the morphological problem can be solved only by utilizing the method of inquiry which we recently adopted for deciding whether *Plasmodium ovale* is to be regarded as a separate species. As regards that parasite, after confirming the finding of Warrington Yorke and Owen that its peculiar morphological characters as described by Stephens remain constant in a series of passages through the human host by direct blood inoculation, we passed it successfully through the insect host (*A. maculipennis*) and found that in the blood of persons infected by their bites its distinctive morphological characters and periodicity of sporulation were the same as they were in the person from whom the mosquitoes had received the infection.

We have conducted precisely the same investigation with three of our strains of the malignant parasite, namely, Rome I and II and Sardinia. The following is an example:

On October 22, 1931, a patient (Case 35) was bitten by one mosquito of a batch which was infected by Professor Missiroli from a crescent case in Rome and sent to us by air-mail. After an incubation period of twelve days the patient developed an attack of malaria which proved to be of malignant tertian type with ring forms of a parasite which, in the peripheral blood, corresponded with the classical description of the Italian malignant tertian type of *P. falciparum*. The strain was passed to another patient (Case 37) by direct blood inoculation on November 17. Crescents became moderately numerous in the blood of this patient, so a batch of *A. maculipennis* was fed daily on the case from the 11th to the 21st December and incubated at 25° C. The results may be summarized as follows:—

Dates of feeding on infecting case	Female crescents in the blood per c.mm.	Exflagellating male crescents per c.mm.	Results of dissection: Days after first feed	Number dissected	Number with oöcysts in stomach	Number with sporozoites in glands
11.12.31	420	120				
12.12.31	240	120				
13.12.31	300	75				
14.12.31	300	180	3rd to 6th	12	1	not examined
15.12.31	300	60	7th to 10th	23	2	not examined
16.12.31	60	40	11th to 13th	5	5	0
17.12.31	240	60	16th to 20th	6	5	0
19.12.31	84	12	21st	2	0	2
20.12.31	72	24	26th to 39th	4	not examined	4
21.12.31	36	12	44th to 46th	4	not examined	4

It will be seen that the dissections up to the tenth day gave an infection rate of only 8% but that later dissections gave a rate of nearly 100%. This higher rate was the result of repeated daily feeds while the blood of the patient contained ripe crescents. Between the seventeenth and the forty-sixth day (December 28 to January 26) twelve patients were successfully infected by the bites of some insects of the batch. Thus a considerable amount of material became available for ascertaining the clinical type of malaria and the morphological characters and periodicity of sporulation of the parasites. We found that the clinical type was typically single or double malignant tertian and that the parasites corresponded morphologically with those in Cases 35 and 37 from which the infection originated and (as in those cases) with the classical description of the Italian malignant tertian (æstivo-autumnal) type of *P. falciparum*.

The same kind of investigation with the Rome I strain (which was the first with which we succeeded in infecting *maculipennis*) and with the Sardinia strain

nad already given a similar result. As yet we have not been successful in making the same complete investigation of our tropical strains, but frequent examinations of the blood of all cases have not enabled us to detect any noteworthy morphological differences between the parasites of the different strains, whether from India, Rome, Sardinia or West Africa. Also (although it is not relevant to the question whether or not there is more than one malignant species) we may mention incidentally here that we have convinced ourselves by the analysis of the temperature charts of our cases which will be described in Section IV, that the fever associated with all the strains is one with a true tertian periodicity, due to groups of parasites which sporulate every forty-eight hours.

Thus, with regard to the results of inquiry into the strains dealt with in the present paper, we have to take up the position that in all our cases only one species of malignant parasite is concerned, namely, the species whose morphological characters and periodicity of sporulation correspond with the classical description of the Italian malignant tertian parasite, *P. falciparum*. This conclusion is the same as the conclusion which was reached by Koch in the inquiry which he conducted (with Pfeiffer and Kossel) in 1898-99 in Italy, East Africa, South-West Africa, West Africa, Central America, the Dutch East Indies and New Guinea, with the object first of studying the alleged different kinds of malignant parasites which were thought to be responsible for æstivo-autumnal fever in Italy, and second of establishing what relation there might be between the Italian and the tropical types of the parasites and the disease. In the series of reports on that inquiry [3] it was made clear that existing confusion as to the unicity or multiplicity of malignant parasites was due partly to the incorrect method by which observers were accustomed to investigate the problem. Instead of relying on the morphology and biology of the parasite they were largely influenced by clinical observations with the result that, having observed many cases of malignant malaria in which a daily febrile paroxysm occurred at approximately the same time, they endeavoured to establish the existence of a parasite which, by sporulating every twenty-four hours, would cause that type of fever. Even to-day this is the point of view from which the subject is sometimes approached. Perhaps this accounts in part for the fact that not all observers who believe in the existence of a "quotidian parasite" are in accord as to its correct morphological description as well as for the opinion of some observers that various descriptions which have been given of the "quotidian parasites" are applicable to the parasite found in cases which clinically are of tertian type. The problem is complicated by an apparent change of view on the part of Marchiafava and others who were the first to describe a separate "quotidian" form. In the latest (1931) edition of their treatise Marchiafava and Bignami admit "only with reserve" the existence of a malignant species having a twenty-four hours cycle and say that the differential microscopic diagnosis between it and the malignant tertian form "is exceedingly difficult and is only possible between the adult forms during apyrexia when the new febrile paroxysm is about to commence. At that time the adult forms of the tertian parasite occupy about one-third of the red corpuscle and are mobile, while those of the 'quotidian parasite' are smaller and are less active in movement or are immobile" [4].

As it is generally agreed that in malignant tertian malaria the size of the adult schizont, as well as the number of merozoites into which it divides, vary in the same case and that at that stage of growth differences of amœboid activity are not easy to detect, we think it is justifiable to conclude from this extract that the argument in favour of the existence of a separate Italian quotidian parasite is not so strong as it seemed formerly to be. Nevertheless, while feeling that the case for the existence of a "quotidian" species of malignant parasite has not yet been made good, we are by no means disposed to think it unlikely that another malignant species will be discovered. The finding that among the "benign" parasites the new

form described and named by Professor Stephens (*Plasmodium ovale*) fulfils all the tests requisite for the establishment of a separate species, shows how necessary it is to keep an open mind on the subject. That finding also indicates how desirable it is that among the "malignant" parasites the form which he described and named in 1914 (*Plasmodium tenue*) should, as soon as possible, be subjected to the same tests.

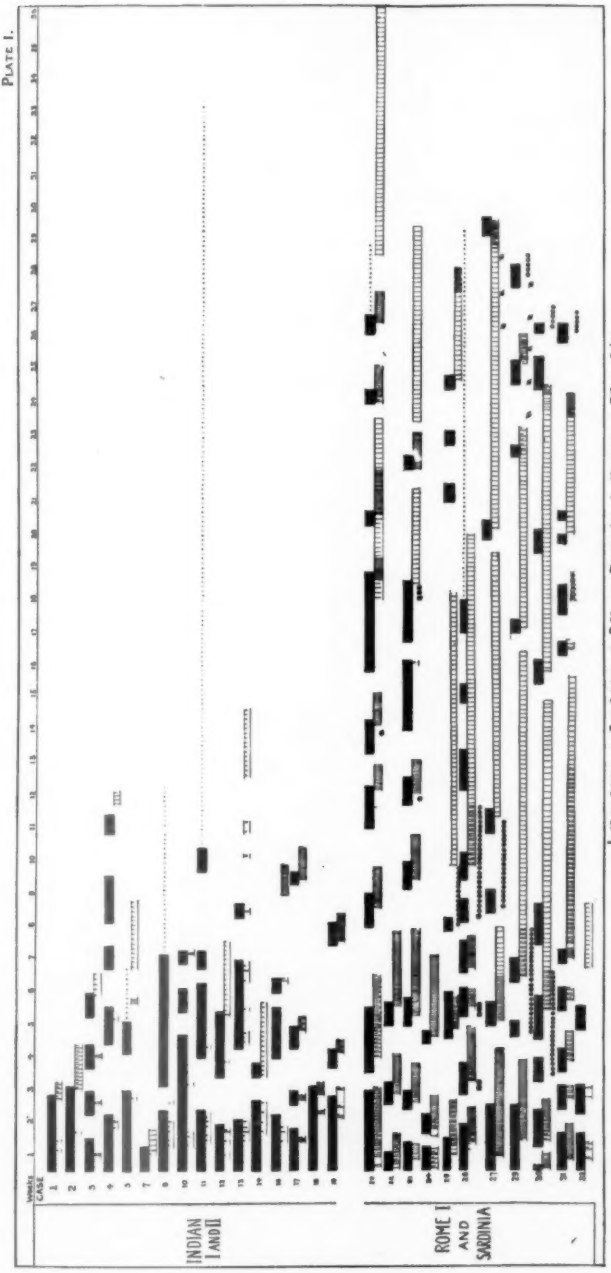
The second problem relates to the biological properties of the parasites of the various strains. All our cases are due to the same species of parasite, but we believe that a biological study of the strains yields definite proof that within the species there are various geographical races which, while not being morphologically different, can be recognized as being distinct by their clinical virulence, immunological reactions and other biological properties.

We shall mention first the biological property of virulence as indicated by a comparison of the clinical severity of cases infected with different strains. Perhaps we can do so best by placing before the reader a diagram (Plate I) of two groups of cases, of which the cases in the first group were infected with the Indian strains I and II and in the second with the strains Rome I and Sardinia. In this diagram the black areas cover the periods of fever in the primary attack and in each relapse, and the upright lines under those areas indicate the amount and duration of quinine treatment, each line representing ten grains and each half-line five grains. The black circles indicate treatment with plasmoquine and other signs indicate treatment with other preparations. It will be seen at once that there are striking clinical differences between the two groups. In the first place it is evident that for cases in the Rome and Sardinia group the amount of quinine treatment was much greater and its duration much longer than for cases in the Indian group. The reason is that cases infected with the Rome or Sardinia strains were very severe, while those infected with the Indian strains were quite mild. When we employ *P. falciparum* for inducing a therapeutic attack of malaria it is our practice to observe several times daily from the first day of fever onwards the clinical signs and the number and character of the parasites and, on the basis of these observations, to administer quinine in doses which we think will be sufficient (but not more than sufficient) to keep the patient free from the risk of hyperpyrexia or other serious complication. Following this practice in our first series of cases (infected with the Indian strains I and II) we were surprised to find how small an amount of quinine sufficed for that purpose. Later we were equally surprised to find in our third and fourth series (infected with the Rome I and Sardinia strains) that full curative doses of quinine given intravenously and by the mouth at frequent intervals were required in order to control the fever and to cause the parasites to disappear from the peripheral blood. On an average, the amount of quinine which we had to administer in order to control a primary attack caused by the Rome or Sardinia strains was eight times as much as was required to control a primary attack caused by either of the Indian strains. The amounts of quinine used for all cases in the two groups were:

Strain of *P. falciparum*	Number of cases	Amount of quinine administered: Total during primary attack	Total during the whole course	Average per case during primary attack	Average per case during the whole course
Indian I and II	19	772 grains	2,233 grains	40 grains	117 grains
Rome I and Sardinia	13	4,343 ,,	21,894 ,,	335 ,,	1,680 ,,

The observation that in every case infected with the Rome and Sardinia strains we were obliged almost at once to resort to intensive quinine treatment, when contrasted with the observation that in no case infected with the Indian strains was it necessary to do so, affords perhaps the best evidence at our disposal in favour of the view that on the ground of clinical virulence the strains must be regarded as being distinct.

PLATE I.

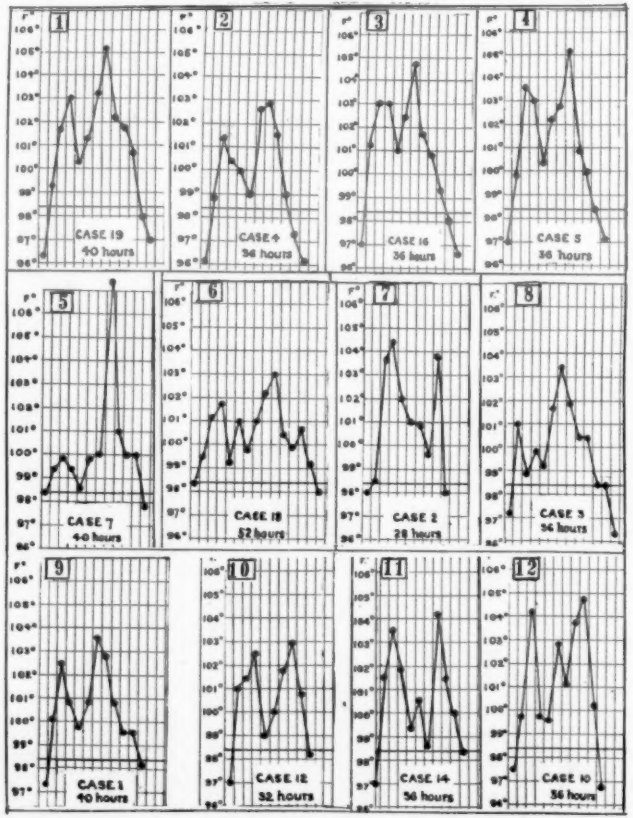

INDIAN I AND II
ROME I AND SARDINIA
1 = 10 grs. Quinine. 1 = 5 grs. Quinine. ■ = R. 36. ● = Plasmoquine. ✎ = Novatoxin. x = 710. o = Erion.
Persistence of parasites without fever.

Early and intensive treatment of cases infected with the Rome and Sardinia strains was called for partly on account of the quick appearance of toxæmic symptoms, partly to interrupt the long periods of sub-continued or remittent fever which were a feature of the primary attack and of some of the relapses in these cases. The duration of these periods of fever can be used as a means of comparing the severity of the cases with the severity of cases infected with the Indian strains. For example, if one studies the temperature charts of all cases throughout the whole course of the infection, one can select for each case the longest period of fever without a fall to the normal temperature. Then one can transfer the recorded temperature curve during that period to another chart side by side with curves of the longest period of fever in other cases, as has been done in the plates facing this page. Plate II is the record during the longest period of fever in twelve cases infected with the Indian strains and Plate III is the same record in eight cases infected with the Rome and Sardinia strains. It is evident that in general the periods are longer and the fever more severe in the group infected by the Rome and Sardinia strains than in the group infected by the Indian strains. The average duration in the former group is seventy-four hours and in the latter thirty-seven hours.

Fever and quinine treatment are criteria by which the severity of the disease can be compared in the two groups on the basis of actual figures. The record illustrated on Plate I provides another indication in that it demonstrates plainly that the cases in the Rome and Sardinia group continued to relapse for a much longer time than those in the Indian group. There are 16 cases in the Indian group and none of them lasted longer than eleven weeks. In the Rome and Sardinia group there are only 11 cases but seven of them lasted more than twenty-one weeks.

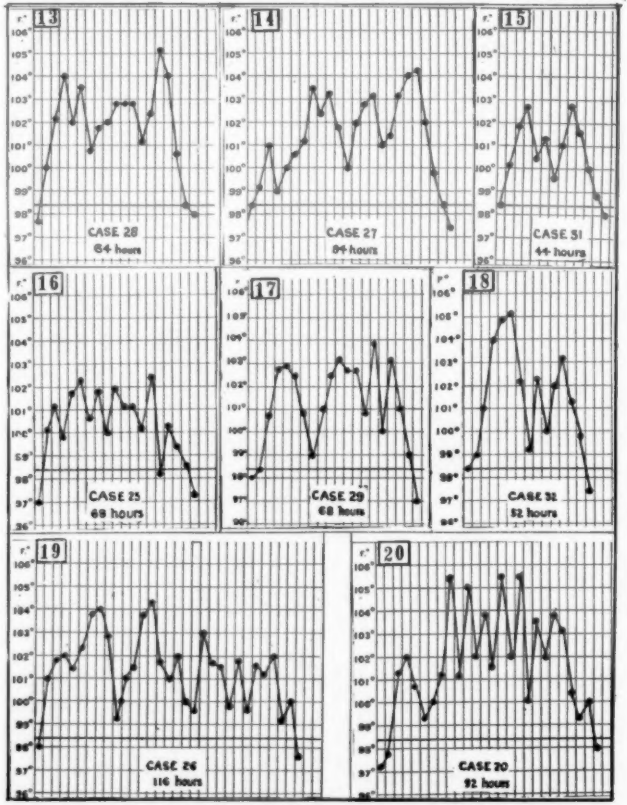
Lastly we must mention a clinical event which was associated with the Rome and Sardinia strains but not with the Indian strains. It was that two of the patients in the former group developed blackwater fever and a third very nearly did so. The circumstances in which this complication arose may be mentioned briefly. As is shown in Plate I we failed entirely to prevent eight of the cases in the Rome and Sardinia group from continuing to relapse. For these cases we were obliged finally to adopt the method of giving 10 grains of quinine every day. In two of the cases this plan was successful in preventing further relapses, but in six it was ineffective. In Cases 26 and 30 further relapses occurred during periods when the daily dose was being taken and in Cases 27, 28, 29 and 31 a relapse occurred whenever we stopped the daily dose in order to ascertain whether a cure had been effected. As, in these cases, plasmoquine simplex and plasmoquine with quinine had also been tried without success, we decided at the beginning of October to ascertain if a cure could be brought about by an intensive course of quinine in large doses, namely gr. xv three times daily for five days. What happened in each case in which this method was tried will be described in detail later. Here it is only necessary to include the following brief record. In Cases 28 and 31 all the doses were taken during the five days and, except vomiting after the evening dose on two or three days, no noteworthy clinical event occurred. In Case 29 the dosage on the second and subsequent days of the course had to be reduced to 30 grains on account of severe tinnitus and visual hallucinations. The patient completed the course with these smaller doses and there were no ill effects. In Case 26 all the doses were taken during the five days but at 8 a.m. on the sixth day the patient had a sharp attack of blackwater with much vomiting. Fever and jaundice followed but there was a good recovery. In Case 30 the patient took the three doses on September 25 and the first of the daily doses on September 26. Shortly after this dose there was a severe attack of blackwater. Vomiting and fever persisted for five days and jaundice was pronounced but there was a good recovery. In Case 27 all the doses were taken for five days but there was much vomiting. The temperature rose above 99° three times during the course and the patient became slightly jaundiced. No hæmoglobin could be detected in the urine but clinically the case resembled what has been described as the "pre-blackwater

PLATE II.



INDIA GROUP.

PLATE III.



ROME AND SARDINIA GROUP.

state." Quinine anti-relapse prophylaxis was not resumed in any of these six cases. Their subsequent history was as follows: Cases 26 and 30 relapsed again with parasites and fever nineteen days and thirteen days respectively after recovery from their attacks of blackwater. Cases 29 and 31 relapsed again with fever and parasites twelve days and thirteen days respectively after completing the intensive quinine course. Cases 27 and 28 had no further relapse. The four cases which relapsed were treated with "erion" (now called *atebrin*) in doses of 0·1 gramme thrice daily for five days. None of them relapsed again.

Evidently in these cases quinine was the exciting cause of the attacks of blackwater fever, but the severity of the repeated relapses which preceded the attacks was the antecedent cause, and the fact that four of the cases relapsed after the attacks supports our thesis that the Rome and Sardinia strains differed from the Indian strains of the same malignant tertian species of parasite in their pathogenicity, virulence and resistance to treatment.

Next we shall mention immunological differences. On January 1, 1930, a patient (Case 9), who had not had malaria previously, was infected (by blood inoculation) with the Indian II strain from Case 8. The attack of malignant tertian malaria began four days later, the fever being in the early days subcontinuous or remittent and then quotidian intermittent. This primary attack which, it was found, could be easily controlled with small doses of quinine, lasted thirteen days. It was followed six days later by a relapse ("recrudescence") which being of a mild character, was allowed to continue, on and off, for a month, during which only a few small doses of quinine were necessary. The patient ceased to have any rises of temperature above 99° F. after the end of February, but parasites could still be found almost daily until April 4. On May 1 the patient was reinoculated with the same strain from Case 13. The result was a mild attack of fever with reappearance of parasites in the blood, but there was a quick recovery without treatment. A similar reinoculation on May 18 caused an even milder attack. On July 4 and on August 8 the patient was reinoculated with the same strain from Cases 14 and 15 respectively, but these reinfections failed to cause any rise of temperature and no parasites could be found in the peripheral blood. We concluded that the patient had become immune to the Indian II strain.

On December 13 the patient was infected (by blood inoculation) with the Sardinia strain from Case 24. This infection resulted, after an incubation period of only three days, in a severe attack for which quinine, in doses of grs. xxx daily, had to be given from the second day onwards. Parasites were still present on the eleventh day of this attack and full therapeutic doses of quinine were continued for eighteen days.

Our records contain other examples of the same kind.

Lastly, on the subject of biological properties, we shall mention an observation and a suggested explanation of it which may or may not be substantiated by further experiments. Briefly, the observation is that we failed entirely to infect our English *maculipennis* with the Indian strains of *P falciparum* but that when we conducted precisely the same experiments with the European strains from Rome and Sardinia we succeeded in preparing batches of infected insects without great difficulty. The list of our failures to infect *maculipennis* with the Indian strains may be given as follows:—

Serial number of case on which the mosquitoes were fed	Number of gametocytes in the blood during the period of feeding (per c.mm.)	Number of times the mosquitoes were fed	Number of mosquitoes dissected	Remarks
1	24	7	17	
5	360 to 1,296	12	45	Ex-flagellating crescents present each day
8	240	4	20	" "
9	36 to 145	9	24	" "
13	1,176 to 5,236	Many	78	" "
13 (2nd experiment)	Up to 6,500	Daily for twelve days	99	" "*

* For details of the feeding experiments in this case see our previous report, "Some General Results of a Study of Induced Malaria in England," page 485.

In contrast to these repeated failures we have records of seven batches of *maculipennis* successfully infected with one or other of four European strains of *P. falciparum*, the mosquitoes of some of the batches being infected to the extent of 100%.

Other recent successful results with a European race of *maculipennis* and European strains of *P. falciparum* are those of Wenyon in Macedonia (1918), Roubaud in France (1918, from cases infected in Macedonia) and Missiroli in Italy. There are also, of course, a number of earlier records. But we cannot find in the literature any instance in which a European race of *maculipennis* has been successfully infected with an Indian or an African strain of *P. falciparum*. Is it possible, we wonder, that within the same species of parasite there may be tropical strains which cannot undergo development in European races of *maculipennis* although these races are efficient hosts of the European strains? Perhaps this is an old problem presented from a new point of view, the old problem being to explain why the same species of anopheles is a good carrier in one country and a non-carrier in another. Hitherto that problem has been examined only from the point of view that there may be different biological races of the same species of anopheles, some of the races being more efficient hosts of the malaria parasite than others. Schüffner, for instance, in a recent paper, when mentioning the names of several well-known species of anopheles which are recognized as being important carriers of malaria in one country but not in another, suggests that to solve this puzzle it has become necessary to investigate the morphological characters of those species anew in order to determine whether any specific or racial differences of morphology can be found which would enable them to be reclassified in a manner that would correspond with their recognized biological differences.[1] We think that having regard to the parasitological point of view it is equally important to study the problem with the knowledge that there are differences in the biological properties of strains of the malignant tertian parasite found in different countries and that the capacity of each strain to infect a named species of anopheles must be separately worked out.

(IV) The Temperature Curve in Malignant Malaria.

The above investigations included, as already mentioned, an analysis, in all our cases, of the temperature curve during each febrile paroxysm. The results enable us (1) to explain the characteristic fever curve of the malignant tertian paroxysm which was discovered and described by Marchiafava and Bignami; (2) to add something to existing observations on the vexed question whether there is or is not a malignant parasite which completes its asexual cycle in twenty-four hours and therefore produces a quotidian type of fever.

On the first problem we may recall that before Marchiafava and Bignami conducted their classical study of malignant (æstivo-autumnal) malaria the character of the fever caused by the malignant parasites was described by most observers as being either quite irregular or as being chiefly of the quotidian type. Marchiafava and Bignami showed, however, that the predominating and most important character of the fever is that it is of tertian type, the onset of each paroxysm being forty-eight hours after the onset of the preceding one. They showed also that the fever is due to a parasite which sporulates every forty-eight hours. But they found that, although the febrile curves of successive paroxysms begin at the same time on alternate days, the duration of each paroxysm is much longer than is the rule in simple tertian fever due to *P. vivax*. Thus a paroxysm beginning, say, at 12 noon on one day, was often so prolonged that it lasted far into the next day, and, by so doing, caused the day of apyrexia which should occur in

[1] Schüffner, "Notes on the Indian Tour of the Malaria Commission of the League of Nations," published in the "Records of the Malaria Survey of India," vol. ii, No. 3, Sept. 1931, p. 346. Swellengrebel and others have written from the same point of view.

true tertian fever to be missing from the chart or to be indicated only by an apyrexial period lasting perhaps eight or ten hours. They described the temperature curve during the paroxysm as follows:

> "The fever begins with a sudden rise, usually reaching or exceeding 40° C. (104° F.); then follows a period, during which the fever curve oscillates within one or more degrees, the most marked rise being that which precedes the crisis. This pre-critical rise is followed by a steep fall of temperature accompanied by a temporary improvement of all the symptoms and then the temperature rises again to its maximum height. Thus in the fever-curve of this tertian type five stages can be recognized, namely, (1) the febrile onset; (2) a period when the curve oscillates; (3) a pseudo-crisis; (4) the pre-critical rise of temperature; (5) the true crisis. The whole paroxysm is usually very long, generally exceeding 24 hours and often lasting 36 or 40 hours."[1]

At one period or another in all our cases there were febrile paroxysms of this characteristic type which, for convenience, may be referred to as "the Marchiafava and Bignami curve."

What is the explanation of this peculiar curve? In considering this question we may note first that the same characteristic curve occurs sometimes (though rarely) in cases of benign tertian malaria due to *P. vivax*, and that we have one instance in which it occurred in an infection with *P. ovale*. These are cases of double tertian type in which the febrile paroxysms caused by the two groups of parasites occur on the same day. One of the paroxysms "anticipates" or the other "retards" until it happens that the two occur at such a short interval that they merge into each other, thus producing a temperature-curve which in its general trend is similar to the Marchiafava and Bignami curve of the malignant tertian paroxysm.

We think that the characteristic curve of the fever paroxysms in malignant tertian malaria is to be explained in the same way.

From this point of view we shall now consider some of the temperature charts of our cases. The charts selected for this purpose are arranged in groups in Plates IV, V and VI.

(1) The simplest form of temperature-curve occurring in malignant malaria is of the "single tertian" type, resembling in all respects the type of curve which is caused by a single group of the benign tertian parasite, *P. vivax*. In Plate IV Charts 21 (Indian II strain), 22 (Sardinia strain), and 23 (Rome II strain) are of this simple type. In Chart 21 the onset of each paroxysm and its peak are almost exactly forty-eight hours apart. In Chart 22 there is evidence of "retardation," for the interval is about fifty-two hours. Chart 23 is an example in which there is evidence of "anticipation," for the interval between the first and second paroxysms is only about forty-four hours, and between the second and third only about forty hours.

(2) Next, there is the type in which there are two dominant groups of parasites instead of only one, the time of sporulation of one of the groups being separated from the time of sporulation of the other group by a considerable interval, often twenty-four hours. Chart 24 (Sardinia strain) is an example of this type. At first there is only one group which causes the paroxysms marked *A*, which are approximately forty-eight hours apart. Then on June 17 the chart shows the entry of a second group which causes the paroxysms marked *B*, which are also at an interval of forty-eight hours.

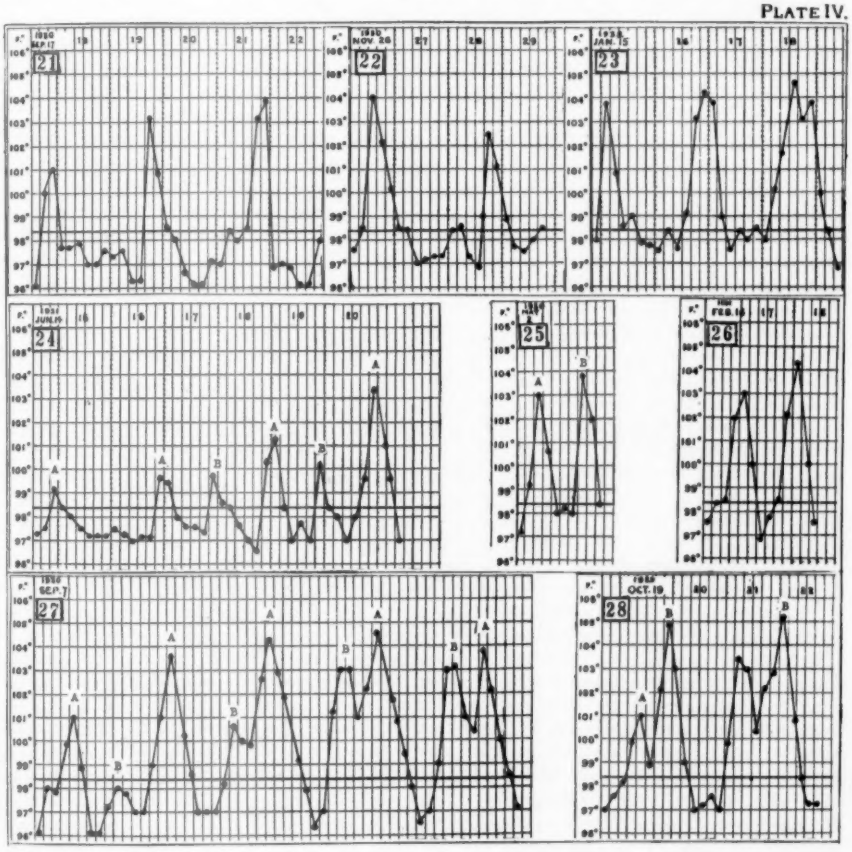
(3) The next is a type in which there are still only two groups of parasites, but there is not so great an interval between the times of sporulation of each group, with the result that the chart shows two separate febrile paroxysms on the same day. Charts 25 and 26 are examples. In both cases the interval between the onset

[1] "La Infezione Malarica," 2nd Ed., 1931, p. 318.

of each paroxysm is only about sixteen hours, and between the end of one paroxysm and the beginning of the next only about eight hours.

(4) In these cases with two groups of parasites it often happens that the time of sporulation of the second group approaches so near to the time of sporulation of the first that the onset of the paroxysm due to the second group begins before the end of the paroxysm which was caused by the sporulation of the first group. When this happens the fall of temperature in the crisis signalling the end of the first paroxysm is met half way and overcome by the initial febrile rise due to sporulation

PLATE IV.



of the second group, and we get the type of temperature curve illustrated in Charts 27 and 28. In many of our charts it can be seen that the paroxysms approach each other day by day (by "anticipation" or "retardation") until what has just been described happens. Inspection of the charts shows that the curve resulting from the fusion of the two paroxysms resembles in general outline the typical Marchiafava and Bignami curve of malignant tertian malaria. The chief difference, perhaps, is in connection with Marchiafava and Bignami's second stage, "a period when the fever oscillates." The two curves illustrated in Charts 27 and 28 do not, in fact,

show oscillations; they show only (1) febrile onset, (2) pseudo-crisis, (3) pre-critical rise, (4) crisis. It is noteworthy, however, that in this respect they are not different from some of the temperature curves illustrated by Marchiafava and Bignami and from some of those illustrated by Craig [5] as typical charts of malignant tertian fever.

(5) But the question whether those temperature curves represent correctly the true Marchiafava and Bignami curve loses its importance when it is recognized that a remarkable feature of malignant malaria is that not only two, but three, and often more, separate groups of the parasite are usually present and continue to persist and to sporulate at their regular times without being suppressed by one or two predominant groups. This is really the most important respect in which the malignant parasite differs from the benign parasites *P. vivax*, *P. malariæ* and *P. ovale*. About 80% of temperature charts of cases infected with one of the "benign" parasites show at some period or other the presence of two groups of the parasite, but among some hundreds of cases we have not seen any in which the chart indicates the presence of three or more groups except during the initial stage before any tolerance has been developed. On the other hand infections with the malignant parasite are quite different in that the charts nearly always show at one period or other of the primary attack, and of relapses, the presence of three or more groups running concurrently and independently, and each causing its own febrile paroxysm. This is one of the chief reasons why in most cases malignant malaria is a more severe disease than benign malaria. On Plate V, Charts 29, 30 and 31 are examples showing the presence of three independent groups. The proof that each group is independent is that by administering quinine at the appropriate time one or other of the groups can be suppressed, in which case the temperature curve reflects only the paroxysms caused by the two remaining groups.

(6) Proceeding in this way one passes on to temperature curves which result from the presence of more than three groups of the parasite, and in doing so one finds, as would be expected, many examples which represent the Marchiafava and Bignami curve in all its details, including the second stage described as "a period when the curve oscillates." From these examples one passes to examples in which the curve is that of the "subcontinued or irregular fevers" which many workers have described. Charts 32 and 33 are of cases with four groups of the parasite, Charts 34 and 35 with five groups and Chart 36 with many groups.

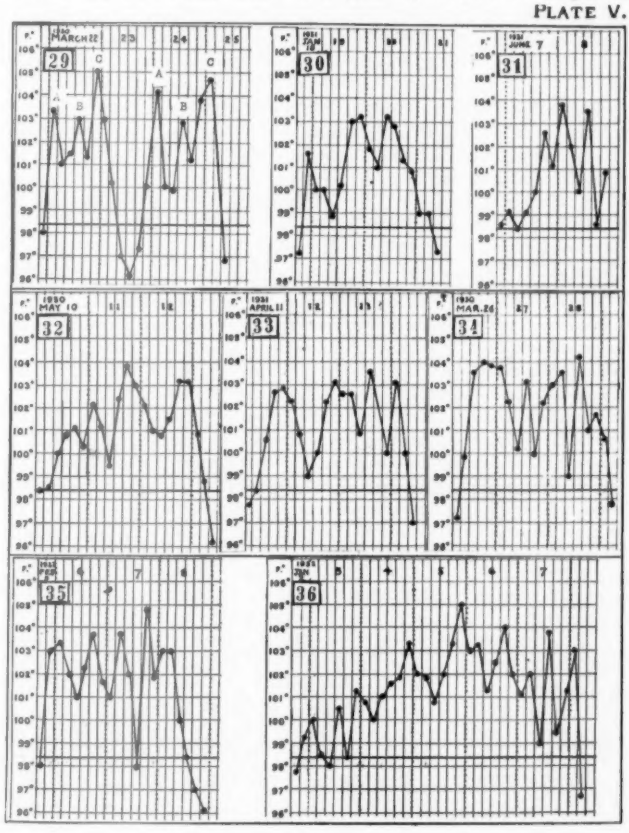
Thus we come to the conclusion that to explain the temperature curves of cases of malignant malaria it is not necessary to affirm, as some authors have done, that this form of malaria may be due to a type of parasite which completes its asexual life cycle in a shorter period than forty-eight hours, nor is it necessary to assume that the duration of the life cycle is variable or irregular. There is, as would be expected from our knowledge of the duration of the life cycle of benign tertian and quartan parasites, some degree of latitude in the number of hours between the onset of each paroxysm, but we have not found in any of our cases that this amount of "anticipation" or "retardation" exceeds twelve hours. We are also less disposed now than formerly to assume that the "irregularity" of some temperature curves in malignant malaria may be due to a tendency for some of the parasites comprising a particular group to complete their asexual cycle quicker than others.[1] On the contrary, since we have had the advantage of studying cases at Horton, where it is a rule to take temperatures much more frequently than every four hours, we are struck by the regularity with which the pyrexial effect of all the parasites in a particular group is manifested at the same time with explosive completeness.

Now about the question whether or not there is a malignant parasite which completes its asexual cycle in twenty-four hours and therefore produces what is called malignant quotidian fever, it will be evident from the above description and

1 As was stated in "Malaria at Home and Abroad," p. 132.

discussion of our cases that, in our view, they can all be explained satisfactorily (and as we think correctly) without postulating the existence of a quotidian parasite. In this matter, too, we are in an advantageous position as compared with previous observers, for in the first place our patients have never previously had opportunities of being infected with malignant malaria and are not liable to reinfections, and in the second they remain under our observation continuously for a year or more and so can be studied in the relapses as well as in the primary attack of the same infection. Thus we are able, when the primary attack in a patient shows a

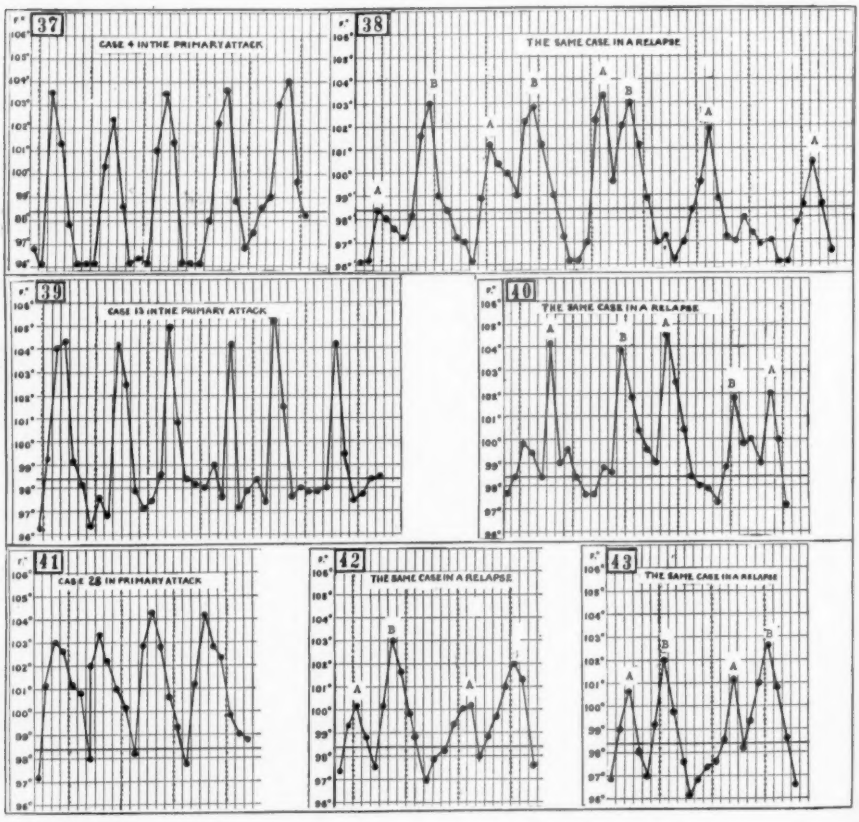
PLATE V.



quotidian type of fever resembling the charts of malignant quotidian malaria illustrated by Marchiafava and Bignami or by Craig, to see whether the same type of fever is reproduced in the relapses. Also we are able, when a case of that kind occurs, to pass the infection by direct blood inoculation or by mosquito bites to other patients and to ascertain the characters of the fever and of the parasites in those new cases. We have done so on several occasions. It is not to be doubted that, if a patient who had quotidian febrile paroxysms in the primary attack develops a "single tertian" type of fever in a relapse, one must conclude that the primary attack was an example of a "double tertian" infection with two groups of parasites sporulating on successive days. Again, if the febrile attack of a patient

who has been infected either by blood inoculation or by mosquito bites from a case of quotidian malaria, is obviously of true tertian type, it has to be concluded that the original infecting case was also of this type, but that two groups of the parasite were present during the period of quotidian paroxysms. On Plate VI, Charts 37 and 38, 39 and 40, and 41 to 43, are examples of cases with quotidian paroxysms in the primary attack, but which were shown to be cases of double tertian fever by the character of the temperature curves during a relapse.

PLATE VI.



(V) The General Course of the Disease in Malignant Malaria.

Until the practice of malariatherapy was introduced it did not often happen that persons who were known to have been bitten by infected mosquitoes could be observed daily from that time onwards and a continuous record kept of the incubation period of the disease, its febrile and parasitic onset and other events leading up to the attack. Nor did it often happen that patients after recovery from a primary attack could be observed continuously for a long period and a record kept of the subsequent course and termination of the case. For these reasons one can seldom find, even in monographs devoted entirely to malaria, a systematic account of cases throughout the whole course of an infection. With regard to benign tertian malaria we were able in our last report partly to fill

that gap in knowledge, and we are now in a position to begin to do the same with regard to the malignant disease.

An important finding in our study of the initial events in infections with benign tertian malaria (*P. vivax*) was the occurrence of cases in which the febrile and parasitic manifestations of an infection caused by the bites of mosquitoes remained latent for six months or more. We recorded twelve such cases in our last report and we have since observed as many more. But there has been no example of this phenomenon among our twenty-three mosquito-infected cases of malignant tertian malaria, although some of the cases were infected by the bite of only one insect on a single occasion. The longest incubation period in our mosquito-infected cases was seventeen days (in four cases), the shortest period six days (two cases), and the mean of all cases twelve days.

About the history of cases after recovery from the primary attack it will be recalled that in our last report we recorded under the headings "recrudescences," "relapses" and "recurrences" the events relating to 107 patients infected with *P. vivax* (by mosquito bites) who were observed continuously for more than six months. An important item in the record was the finding that, apart from the recrudescences and relapses which occurred earlier than twenty-four weeks after recovery from the primary attack, there occurred in 30% of the cases a recurrence of the disease at a later period. We found that the recurrence happened, in most cases, about twenty-seven weeks after recovery from the primary attack, and that it seemed to bear a definite relation, in point of time, to the date of infection by mosquitoes, being in general between thirty and thirty-five weeks after that event.

Particularly with the phenomena of "recrudescences," "relapses" and "recurrences" in mind it is obviously of interest to ascertain the usual sequence of events following recovery from primary attacks of the malignant tertian disease.

Unfortunately we are not able, for two chief reasons, to deal with the subject in the same way as we did in our account of benign tertian malaria. The first reason is that as yet we have only seven mosquito-infected cases that have been observed for more than a year. The second is that in October, 1931, we began to treat some of our malignant cases with "erion" (now called *atebrin*) instead of with quinine, and by so doing unavoidably prevented conclusions about them being comparable with the conclusions applicable to our previous cases. It is not yet known whether, if "relapses" and "recurrences" occur in malignant tertian malaria, *atebrin* administered for the cure of the primary attack will prevent them or not, but, as we shall see in the next section of this paper, it is so much more effective than quinine for curing the primary attack and for preventing "recrudescences" in this form of malaria that cases treated with it and cases treated with quinine cannot justifiably be included in the same category.

In view of these limitations what we can say about later events in malignant tertian malaria may be summarized as follows:—

(1) Malignant tertian malaria differs from benign tertian in that one cannot limit "recrudescences" to events occurring within a period of eight weeks after recovery from the primary attack as we did with regard to the benign tertian disease. For although it is true that most cases of malignant tertian malaria cease to recrudesce within two months after recovery from the primary attack, a number still continue to do so for a much longer period. Thus, in these cases, the period during which "recrudescences" are still occurring merges without a well-defined break into the period which, in connection with benign tertian malaria, we called the period of "relapses," and indeed, in some cases, into the period of "recurrences." It is possible, of course, that what we call "relapses" and "recurrences" may be a much later event in infections with *P. falciparum* than in infections with *P. vivax*. Ziemann seems to be of this opinion, for, on p. 191 of his monograph published in the 1924 edition of Mense's "Handbuch der Tropenkrankheiten," he writes: "The author himself had a recurrence of pernicious fever eighteen months after leaving

the Cameroons, having been in a non-malarious district all the time." Marchiafava and Bignami, on the other hand, seem to hold that what we call "relapses" and "recurrences" do not occur in malignant tertian malaria, for they write on p. 328 of the 1931 edition of their work: "If no reinfections occur, the existing infection, after several winter relapses, dies out in the following spring or summer." This, as everyone knows, was also what happened in infections with *P. falciparum* contracted during the war. The only observation which we can add as a result of our present study of the induced disease is that, although some of the seven mosquito-infected patients whom we have had under continuous observation for a year or more since their recovery from the primary attack had many "recrudescences" during the first six months of that period, none has subsequently shown a "relapse" or a "recurrence."

(2) Malignant tertian malaria also seems to differ from benign tertian malaria in that, as regards the occurrence of "recrudescences" no difference is apparent between the disease caused by direct blood inoculation and the disease caused by the bites of infected mosquitoes. In blood-infected cases of malignant tertian malaria, recrudescences occur after the primary attack has been cured by quinine to the same extent as they occur in mosquito-infected cases. This being so, it is justifiable, we think, to utilize our blood-infected cases, as well as our mosquito-infected cases, for observations on "recrudescences" following a primary attack of malignant tertian malaria. If we do so and if at the same time we exclude cases which were fatal in the primary attack and cases in which the primary attack or the first recrudescence was treated with *atebrin* instead of quinine, our total cases available for observations on recrudescences number thirty-six, of which seventeen were infections with the Indian strains, seven with the Rome strains, eight with the Sardinia strain, and four with the West African strains.

(3) Among the thirty-six cases just mentioned there were seven in which no recrudescence followed cure of the primary attack. The events in the twenty-nine cases which are left may be tabulated as follows:—

Serial number of case	Number of recrudescences	Period covered by the primary attack and recrudescences	Average fever-free interval between the recrudescences (in days) †	Subsequent relapses or recurrences	Total period under observation from the beginning of primary attack
3	3	5 weeks	6	0	4 years 8 months
4	4	11 ,,	9	0	2 ,, 6 ,,
5	1	5 ,,	7	0	2 ,, 6 ,,
8	2	6 ,,	5	0	2 ,, 4 ,,
9	1	7 ,,	6	0	2 ,, 4 ,,
10	2	6 ,,	5	0	2 ,, 1 ,,
11	3	10 ,,	11	0	2 ,, 1 ,,
12	1	5 ,,	11	0	2 ,, 1 ,,
13	5	12 ,,	9	0	2 ,,
14	1	3 ,,	6	0	1 ,, 11 ,,
16	3	8 ,,	8	0	1 ,, 8 ,,
17	3	9 ,,	15	0	1 ,, 8 ,,
19	2	7 ,,	14	0	1 ,, 8 ,,
20	8	26 ,,	13	0	1 ,, 6 ,,
22	2	5 ,,	11	0	1 ,, 5 ,,
23	7	22 ,,	14	0	1 ,, 5 ,,
24	2	4 ,,	10	0	1 ,, 5 ,,
26	11	32 ,,	8	0*	1 ,, 2 ,,
27	4	20 ,,	16	0	1 ,, 2 ,,
28	5	24 ,,	14	0	1 ,, 1 ,,
29	6	27 ,,	14	0*	1 ,, 0 ,,
30	7	26 ,,	11	0*	1 ,, 0 ,,
31	8	26 ,,	7	0*	1 ,, 0 ,,
32	2	5 ,,	8	0	10 ,,
33	2	9 ,,	13	0	10 ,,
34	1	4 ,,	6	0	9 ,,
37	4	10 ,,	11	0*	5 ,,
40	5	13 ,,	11	0	4 ,,
42	6	12 ,,	15	0	4 ,,

* The last recrudescence in these cases was treated with *atebrin*.

† We have omitted a few long intervals during which recrudescences were prevented by daily doses of quinine gr. x.

(4) According to the results set out above, quinine treatment of the primary attack brings about a permanent cure in less than 20% of cases of malignant tertian malaria as compared with 50% for cases of the benign tertian disease. The usual sequence following recovery from the primary attack is a series of recrudescences occurring at intervals of approximately ten days. Taking one strain with another the number of these recrudescences resulting from a single infection is, on an average, four, but there may be as few as one or as many as eleven. The recrudescences are obviously brought about by repetition of the process which led to the primary attack and are due to the persistence and multiplication of the ordinary asexual parasites. As yet we have no evidence of the occurrence in malignant tertian malaria of "relapses" or "recurrences" in the sense in which we used those terms in connection with the benign tertian disease. The duration of the disease as manifested by febrile attacks is seldom less than a month and seldom longer than six months. As a general rule the duration of the disease as manifested by febrile recrudescences and its duration as manifested by finding parasites in the peripheral blood are approximately the same, but about 20% of patients who contract a malignant tertian infection for the first time continue to harbour parasites for a longer or shorter period after apparently complete clinical recovery. Some examples will be given in a later paragraph.

(5) Clinically, as has just been said, malignant tertian malaria, in its general course, is an acute disease consisting of a severe primary attack followed by several less severe recrudescences occurring at relatively short intervals. So far as we know at present this comprises all the febrile manifestations resulting from a particular infection. In this respect it differs strikingly from benign tertian malaria in which there are, in addition to recrudescences, much later manifestations which we call "relapses" and "recurrences." Thus malignant tertian malaria is correctly described as an acute disease as opposed to benign tertian which is a chronic one. In natural malignant tertian malaria the greater severity of the primary attack as compared with the first and subsequent recrudescences was observed by Koch, Marchiafava and many later workers and the same is true of the induced disease. The difference is so marked that it can be said definitely that only in the primary attack is there a grave risk of pernicious symptoms—always excluding, of course, blackwater fever, which is a manifestation not associated with abundance of parasites and their active sporulation as are other pernicious complications. The quickly declining severity and duration of the recrudescences are well shown in the two or three temperature charts of mosquito-infected cases which are reproduced as an appendix to illustrate the general course of the disease throughout the whole of a particular infection. It is a point of importance in treatment as we shall endeavour to show in the next section.

(6) The parasitic infestation, judged by the number of ring forms present in the peripheral blood, is also greatest in the primary attack and diminishes in each recrudescence. The following examples are based on the mean figures of the highest counts of ring forms recorded (per 100 fields of the microscope) in the primary attack and in each recrudescence.

	Primary attack	First recrud.	Second recrud.	Third recrud.	Fourth recrud.	Fifth recrud.	Sixth recrud.	Seventh recrud.	Eighth recrud.
Case 10	97	50	30	20	—	—	—	—	—
,, 4	157	67	57	18	—	—	—	—	—
,, 11	420	61	10	7	17	5	4	—	—
,, 13	417	53	15	11	35	8	—	—	—
,, 26	157	115	36	8	22	2	1	—	—
,, 28	252	33	27	13	9	8	2	—	—
,, 20	88	34	36	26	48	28	4	2	1
Mean of 20 cases	161	37	28	21	48	24	10	2	

The higher count in the fourth recrudescence happens because in most cases the fourth and later recrudescences are mild enough to permit quinine to be withheld. When this is done more parasites can be found in the peripheral blood, but the practice has the good result of allowing the patient more quickly to acquire the tolerance which is indicated in the small counts for the sixth and later recrudescences.

The above findings are of service in interpreting the significance of parasite counts at different age-groups made during malaria surveys in the field, as well as in coming to a decision in individual cases of malaria, whether one is dealing with a primary attack or a relapse.

(7) Cessation of febrile attacks does not indicate in all cases the termination of the general course of the infection, for it happens sometimes that parasites can be found in the peripheral blood for quite a long period after the last febrile recrudescence. We have the following examples among the fifty-four cases with which this paper is concerned.

	Period during which parasites were still found in thin films after recovery from the last febrile recrudescence	
	Rings	Crescents
Case 5 ...	7 days ...	11 days
,, 8 ...	77 ,, ...	53 ,,
,, 9 ...	36 ,, ...	21 ,,
,, 11 ...	159 ,, ...	9 ,,
,, 20 ...	15 ,, ...	0 ,,
,, 26 ...	79 ,, ...	46 ,,
,, 28 ...	21 ,, ...	0 ,,
,, 35 ...	6 ,, ...	10 ,,
,, 42 ...	37 ,, ...	36 ,,
,, 54 ...	8 ,, ...	13 ,,

(8) The incidence of the sexual forms of the parasite (crescents) during the various stages of a malignant tertian infection is also a subject of great interest and importance, but it would take too long to deal with it in the present paper.

(VI) Treatment.

Treatment by quinine.—Including the observations recorded in our previous papers with those made during the present study, we can now say that the following conditions influence the therapeutic effect of quinine on the clinical and parasitological course of malaria :—

(1) The mode of infection.

(2) The degree of natural susceptibility or natural resistance to malaria possessed by the individuals under treatment.

(3) The degree of " tolerance " or " immunity " to malaria which the individuals have acquired before quinine treatment was begun.

(4) The species of parasite concerned.

(5) The virulence of the particular geographical race or strain of the parasite.

(6) The dose of the infection.

If an endeavour is being made to give a sufficient account of the antimalarial effect of quinine, or to compare its efficacy with that of other drugs, it is also necessary to consider separately its effect on the different stages of the parasite in the human host, namely, the sporozoites which the mosquito injects, the asexual forms which are responsible for the fever and other symptoms, the sexual forms which are destined to continue the life-cycle of the parasite in the insect host, and the hypothetical developmental forms in the internal organs which, in benign tertian malaria, are thought to be responsible for the manifestations at a long interval which we call recurrences.

We may remark on the above conditions as follows :—

(1) About the mode of infection it is known that in benign tertian malaria there is a striking difference between the therapeutic effect of quinine in cases induced by

blood inoculation and in those induced by the bites of infected mosquitoes. We find that in malignant tertian malaria this difference does not exist. This will be appreciated from the following comparison of cases :—

Cases infected with the Rome I strain.

Serial No. of case	How infected	Duration of primary attack	Quinine treatment for primary attack	No of re-crudescences	Total quinine treatment
Case 20	Mosquitoes	17 days	474 grains	8	2,585 grains
,, 26	Blood	10 ,,	262 ,,	11	2,482 ,,
,, 22	Mosquitoes	4 ,,	204 ,,	2	430 ,,
,, 28	Blood	7 ,,	330 ,,	5	1,515 ,,

Cases infected with the West African I strain.

Case 33	Mosquitoes	10 days	35 grains	2	270 grains
,, 34	Blood	10 ,,	25 ,,	1	260 ,,

Cases infected with the Sardinia strain.

Case 29	Mosquitoes	14 days	526 grains	6	1,936 grains
,, 27	Blood	14 ,,	630 ,,	4	2,355 ,,
,, 30	Mosquitoes	4 ,,	90 ,,	7	1,730 ,,
,, 23	Blood	6 ,,	80 ,,	7	2,245 ,,

(2) About the condition of being naturally susceptible or naturally refractory to malarial infection there are several examples in our series of malignant tertian cases which support the correctness of the classification of individuals into those who are " very susceptible," those who are " quite refractory," and those who are " normally susceptible " to the same strain of the parasite. For instance, all the patients in the series " Indian II strain " were infected in the same way and with approximately the same dose, but the reaction in several patients was more severe than in the majority and in several others it was milder than in the majority. The fatal case in this group (Case 6) was obviously " abnormally susceptible," for the infection very quickly developed in an explosive (" fulminant ") way with numerous ring forms and many pre-sporulating forms in the peripheral blood. The fatal case in the series " Sardinia strain " (Case 21), in which the infection was by mosquitoes, was of precisely the same " abnormally susceptible " type, numerous ring and pre-sporulating forms being found on the seventh day, although the patient had been on quinine treatment from the fourth day onwards. Among the cases which can be classed as " refractory " may be mentioned, in the Indian group, Case 10, in which the patient, as the result of the first infection, developed only a minor parasitic primary attack (parasites 2 per 100 fields) without fever and, as the result of a second infection a month later, only a similar non-febrile attack (parasites 6 per 100 fields), and finally as the result of a third infection with blood inoculated *intravenously* a febrile attack which was cured by administering only nine grains of quinine.

(3) In malignant tertian malaria, as in benign tertian, the degree of " tolerance " or "immunity " acquired by the patient has a great influence on the subsequent course of the disease. The first recrudescence is less severe than the primary attack, and each subsequent recrudescence is less severe than preceding ones. Finally the patient becomes so tolerant of the parasitic invasion that although parasites may still be present in sufficient numbers to be found in thin films of peripheral blood they cause no fever or other obvious clinical sign. Moreover, we described in Section III how persons reinfected several times with the same strain of a malignant tertian parasite become completely " immune " to that strain, and in Section V we mentioned the observations of Koch, Marchiafava and others to the effect that tolerance to an infection with malignant tertian parasites is so quickly acquired that, as a rule, the risk of pernicious symptoms is confined to the primary attack.

This being so, it seems clear that, whenever it is possible to do so, it is in the best interest of patients suffering from malignant tertian malaria to use quinine

only very sparingly for the treatment of recrudescences and even (provided that there are good nursing and laboratory arrangements) to withhold this drug entirely in some of the recrudescences with the object of allowing the patient to acquire the tolerance which alone (in the absence of a drug capable of completely eradicating the infection) seems to bring about permanent recovery. The following is a brief record of cases in which we have endeavoured to apply this principle:—

Case 4.—(Indian II strain). Primary attack treated with small doses of quinine lasted twelve days. First recrudescence treated with only one dose of 2½ grains of quinine lasted eight days. Second recrudescence with no quinine treatment lasted four days. Third recrudescence with no quinine treatment lasted ten days. Fourth recrudescence with no quinine treatment lasted four days. Two days after recovery from this recrudescence a short course of quinine was given. There was no further recrudescence.

Case 8.—(Indian II strain). Primary attack treated with small doses of quinine lasted fifteen days. First recrudescence with no quinine treatment lasted three days. Second recrudescence with no quinine treatment lasted twelve days. No "after-treatment" was given, and although parasites could still be found from time to time for nearly three months there was no febrile or other obvious clinical manifestation.

Case 9.—(Indian II strain). Primary attack treated with small doses of quinine lasted thirteen days. First recrudescence was mild but lasted "off and on" for twenty-nine days. Only one dose of 1 grain of quinine was given. There were parasites without fever for thirty-six days but no febrile recrudescence. After parasites could no longer be found the patient was reinfected with the same strain and reinfection was repeated three times during a period of four months, during which no quinine treatment was given. The patient became quite immune to the strain used.

Case 10.—(Indian II strain). Primary attack treated with small doses of quinine lasted twenty-nine days. First recrudescence with no quinine treatment lasted five days. Second recrudescence with no quinine treatment lasted three days. After recovery from this recrudescence one dose of quinine gr. xx was given. There was no further recrudescence.

Case 11.—(Indian II strain). Primary attack treated with small doses of quinine lasted thirteen days. First recrudescence, during which only one dose of two grains of quinine was given, lasted sixteen days. Second recrudescence with no quinine lasted four days. Third recrudescence with no quinine lasted five days. No "after-treatment." There was no further febrile manifestation but parasites could still be found from time to time for 159 days. It was shown during this period that they could be made to disappear from the peripheral blood very quickly and for many days by giving one small dose of quinine (gr. v).

Case 28.—(Rome I strain). Primary attack treated with large doses of quinine (gr. xxx daily for eleven days) lasted seven days. First recrudescence treated the same way lasted ten days. Second recrudescence with no quinine treatment lasted three days. Anti-relapse "after-treatment" comprising a course of plasmoquine simplex (0·04 g. daily) for thirteen days followed by a course of quinine gr. v twice daily for two months. During this course no recrudescence occurred, but a third recrudescence began twenty days after its completion. No quinine treatment was given, and it lasted four days. A fourth recrudescence with no quinine treatment lasted three days, and a fifth, also with no treatment, three days. Probably complete recovery would have soon occurred, but as the infection had already lasted more than six months it was thought advisable to resume daily "anti-relapse" doses of quinine gr. x. No further recrudescence occurred.

Case 42.—(Rome II strain). Primary attack treated with large doses of quinine (gr. xxx daily for seven days) lasted seven days. First recrudescence with no quinine treatment lasted two days. Second recrudescence with large doses of quinine as before (gr. xxx daily for seven days) lasted six days. Third recrudescence with no quinine treatment lasted four days. Fourth recrudescence with no quinine treatment lasted one day. Fifth with no quinine lasted four days. Thereafter parasites persisted but without appreciable febrile manifestations.

Case 35.—(Rome II strain). Primary attack treated with large doses of quinine (total gr. 120) lasted five days. First recrudescence which began seven days later was treated with *atebrin* (0·3 g. daily for five days). There was no further recrudescence. The patient was reinfected with the same strain three months later. The primary attack due to this reinfection treated with quinine in doses of gr. xv to gr. xxx daily for five days lasted nine days. Parasites persisted, but no febrile recrudescence occurred, so a month later reinfection with the same strain was repeated. It caused an attack which, with no quinine treatment, lasted five days and was followed by a recrudescence which, with no quinine treatment, lasted three days. There were no further febrile attacks, but parasites persisted a long time.

It seems to us justifiable to conclude from this record that the advice invariably given in textbooks to the effect that in malignant tertian malaria one must set about giving quinine as soon as the diagnosis is made may not always be in the best interests of the patient. It is clear, also, that any attempt to ascertain what system of quinine treatment is best cannot avoid yielding a misleading result unless the therapeutic trials are made on cases which are in exactly the same stage of the disease. This is an axiom which (doubtless unavoidably) is nearly always neglected in large scale inquiries into treatment. It was not laid down as one of the "steps necessary to test the efficacy of any treatment" in the recently-completed inquiry into the treatment of malarial fevers conducted under the auspices of the Indian Research Fund Association, and it is a chief reason why systems of treatment based on experience in hospitals for tropical diseases situated in non-malarious countries may give poor results when practised in the tropics. For example, Ruge states that at the Tropical Institute and Hospital in Hamburg among 2,867 cases of malignant tertian malaria admitted in twenty-six years only ten were examples of a true primary attack [6]. It is often stated that malignant malaria is easier to treat in hospitals so situated (as in England for example) than in the tropics, but the true reason does not seem to have been recognized. Stephens attributed it to "climate," which he said "totally changes the aspect of malaria" [7]. Low, on the other hand, has said that "the exact reason is not very evident; there is something else, apart from the chances of reinfection" [8]. Probably the reason is simply that the cases of naturally acquired malignant tertian malaria admitted to hospitals in England are always examples of recrudescences, never of primary attacks. Our failure to get as good results with the "Sinton treatment" (quinine + alkali) as were reported in the Indian inquiry may be due in part to the same reason, for all our trials are on persons who are known definitely to have the disease for the first time, while in the Indian trials it was not found practicable to do more than to endeavour "where possible, to draw a distinction between old chronic infections and those probably of recent origin" [9].

(4) Except when the chief object of an inquiry is to obtain information for prescribing what is called a "standard treatment" applicable to "malarial fever as a whole" the necessity of investigating separately the therapeutic effect of quinine on each of the different species of the parasite is everywhere insisted upon. We have already indicated in Section III, and later, how much more difficult it is to cure with quinine the primary attack of some infections with *P. falciparum* than it is to cure the primary attack of any infection with *P. vivax*. We need not pursue the subject further here except to say that from the point of view of economy in the consumption of quinine the importance of prescribing a separate system for each parasite rather than a "standard system applicable to all" has become much greater since the discovery of *P. ovale*. This parasite, so far as we know it at present, is so "benign" that even in primary infections caused by a large dose of sporozoites or of infected blood the tendency to "spontaneous recovery" is so marked that it is hardly ever necessary to do more than assist it by giving one or two small doses of quinine. Some cases show a quite surprising absence of clinical signs even in the primary attack. Recently we have had one in which the patient,

although he had never previously had malaria, failed to develop any febrile manifestation until more than forty parasites per 100 fields were present in the peripheral blood.

(5) No one who has studied in the same ward cases of malaria infected with *P. falciparum* and cases infected with *P. ovale* can fail to be convinced that the former species of the malaria parasite possesses the biological property of being much more virulent to the human host than the latter. In Section III we have endeavoured to show that a striking difference can also be observed between the clinical virulence of different geographical races or strains of the same morphological species of parasite, and that the difference is particularly apparent between various races of *P. falciparum*. Evidently this finding has an important bearing on treatment. We see in it the probable explanation of contradictory observations on the therapeutic efficacy of the same form of treatment conducted in different countries and on the comparative value of different systems of quinine administration, as well as of divergent views on the relative amenability to quinine treatment of the different species of the malaria parasite. If the two Indian strains of *P. falciparum* with which we have worked are common strains in that country it is not surprising that in India it is frequently stated that infections with this parasite are easily cured,[1] or that a " standard quinine course " employed there gives better results than in parts of Africa or Italy or Eastern Europe. Our observations introduce a new difficulty in the subject of chemotherapeutic tests of antimalarial drugs, for it is obvious that we must now limit comparative tests to patients infected not only with the same species but also with the same strain of the parasite. A report of highly successful results with a new antimalarial preparation would be valueless unless it were shown at the same time that the cases on which the report was based were not infected with a strain which could be cured as successfully by a few small doses of quinine.

(6) As to the influence of the dose of infection, it will be recalled that as regards benign tertian malaria statistical analysis relating to 746 cases in which the numbers of bites by infected mosquitoes were known showed that the dose has a definite but not very striking influence. We think that in the malignant tertian disease the effect is considerably greater, but as yet our mosquito-infected cases are too few for statistical study. All we can say is that we find in general that the primary attacks of cases infected by the bites of many infected mosquitoes are more difficult to control and are of longer duration than of cases infected by the bites of only one or two insects.

The principal conclusion which we draw from the above summary is that the time has passed when it can be regarded as satisfactory or sufficient to make a diagnosis of " malaria " and to begin at once a " standard quinine treatment." Nor is it sufficient to know the species of parasite concerned and to prescribe the particular system of quinine treatment which up to now has been considered most appropriate for an infection of that type. Evidently what one must do now is in the first place to endeavour to learn much more about the case than (in our experience) it has usually been the practice to learn hitherto. In this connection field workers and hospital physicians in all malarious parts of the world should endeavour as soon as possible to add to existing information on the clinical virulence of the particular strains of *P. falciparum* prevalent in the countries where they work. Are all the strains in India as mild as those reported in this paper and are all the Italian strains as virulent? If a patient is able to say in what place he contracted the infection shall we have at hand information indicating what will be the probable course of his illness? From the history and from the laboratory report can one say whether he has a primary attack or a recrudescence and, if the latter, how many more is he

1 " *P. falciparum* in its schizogony cycle is admittedly the most amenable of the three species to quinine therapy," Knowles, Senior White and Das Gupta, *Indian Medical Research Memoirs*, No. 18, December, 1930, p. 7.

likely to have before permanent recovery? From all the information obtained, would one be justified in withholding quinine for a short period to ascertain by frequent blood examinations and clinical investigation whether the parasitic infestation and signs and symptoms are diminishing "spontaneously" or are becoming more pronounced? And if available information is insufficient, should one begin treatment with relatively small doses of quinine to ascertain what dosage may be the least that will still permit the patient to acquire an immunity against further recrudescences, or should one stop the attack at once by giving daily doses of 20 or 30 gr. and by so doing deprive him of the opportunity of gaining that tolerance? Then again, when the attack is over, should one advise "anti-relapse treatment" of 10 gr. of quinine daily for three or four months or longer and, when one does so, should the patient be advised that, to avoid a possible risk of blackwater, he should not increase the daily dose if (despite this treatment) he gets another recrudescence?

These are some of the problems of quinine treatment that have arisen during the present study: we realize fully that the solution of some of them is still far to seek.

Treatment by "erion" (now called *atebrin*).—In October, 1931, we received for clinical trial from Professor Schulemann, of the Bayer Products Research Laboratories, Elberfeld, a supply of the new synthetic antimalarial preparation which at that time was under laboratory trial with the provisional name "erion" and has since been issued with the trade name *atebrin*.

Our first trials with it were on the four cases of malignant tertian malaria which, as already recorded in Section III, continued to relapse for more than six months after their primary attacks. Three of them were cases infected by mosquitoes and one was a case infected by blood inoculation. All had been treated with large doses of quinine in the primary attacks and in each relapse, and all had received anti-relapse quinine treatment (gr. v twice daily) in the intervals between the recrudescences. The relapses, for which they were treated with *atebrin*, occurred between twelve and nineteen days after an intensive course of quinine treatment, which in two of the cases had brought on an attack of blackwater fever. The following are some particulars of the trial:—

No. of case	Strain of *P. falciparum*	How infected	Stage of disease treated with atebrin	Dosage	Result	Period of observation since atebrin treatment
Case 26	Rome I	Blood	In the 11th recrudescence	0·3 g. daily for 5 days	Quick disappearance of fever and parasites and no subsequent recrudescence	27 weeks
Case 29	Sardinia	Mosquitoes	In the 6th recrudescence	,,	,,	28 weeks
Case 30	Sardinia	Mosquitoes	In the 7th recrudescence	,,	,,	28 weeks
Case 31	Sardinia	Mosquitoes	In the 8th recrudescence	,,	,,	28 weeks

For the above trial there were no cases of the same type and at the same stage of the illness to serve as controls. It is possible, though not probable, that the same permanent cure would have resulted if the recrudescence had been treated with quinine or even if no treatment had been given. But in view of the risk of blackwater in these cases we welcomed the opportunity of treatment with another drug than quinine or plasmoquine and were pleased at the good result.

The next trial was on a case which was infected by direct blood inoculation from Case 26 (Rome I strain) which appears in the above tabular statement. We were aware that the four patients previously infected with the Rome I strain either by the bites of mosquitoes or by blood inoculation (despite early and almost continuous treatment with quinine in therapeutic doses) had had severe primary attacks followed by from two to eleven recrudescences, and we were anxious to see what might be the effect of the new drug administered (as quinine was administered) in the beginning of the primary attack. The dosage given was 0·3 gramme (three tablets all given at the same time) at 10 a.m. daily for five days commencing on the

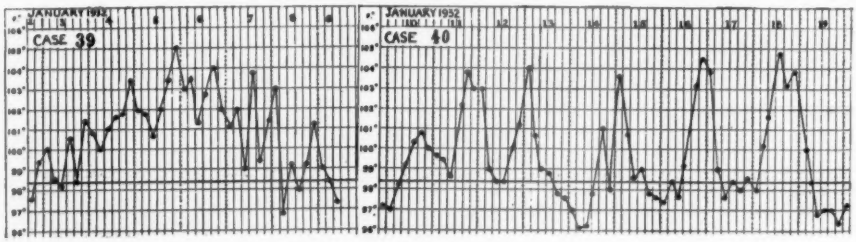
second day of fever. The result was surprising, for although on the third day the expected febrile paroxysm was rather prolonged with temperatures from 104·2° to 104·8°, for which tepid sponging was repeatedly required, this was the last febrile paroxysm that occurred. The parasites which had risen to forty per 100 fields on the third day fell to twenty-four on the fourth and to eight on the fifth; thereafter none could be found. The patient has since been under continuous observation for twenty-three weeks without a recrudescence. The duration of the case, as indicated by fever and parasites, was therefore only five days, as compared with durations respectively of twenty-six weeks, five weeks, thirty-two weeks and twenty-four weeks in the other four cases infected with the same strain but treated with quinine.

Our next trials were on cases infected with the Rome II strain, with which we had successfully infected a batch of mosquitoes. We decided as a first experiment that two patients should be infected by the bites of mosquitoes at the same time and that the primary attack and any subsequent recrudescences of one patient should be treated with quinine and the primary attack and any subsequent recrudescences of the other patient with *atebrin*. The details of infection were:—

Case 39.—No malaria previously. Bitten by eighty-seven mosquitoes (Rome II strain) between the 26th and 31st December. The primary attack began on January 2 (incubation period seven days).

Case 40.—No malaria previovsly. Bitten by fifteen infected mosquitoes on January 1. The primary attack began on January 9 (incubation period eight days).

The dose of infection of Case 39 was heavier than of Case 40, but how much heavier is not certain as it was not until the 31st that sporozoites were present in the glands of all mosquitoes dissected. We decided to treat Case 39 (bitten by eighty-seven mosquitoes) with *atebrin*, and Case 40 (bitten by fifteen) with quinine. Thus, at the start of the experiment, the advantage was with quinine rather than with *atebrin*. As it turned out this was a fortunate decision, for in Case 40 (which was to be treated with quinine) the primary attack appeared to be less severe than in Case 39 which was to be treated with *atebrin*. This can be seen at a glance in the temperature charts of the primary attack in the two cases which are given below:—



The treatment for the primary attack was:—

CASE 39.

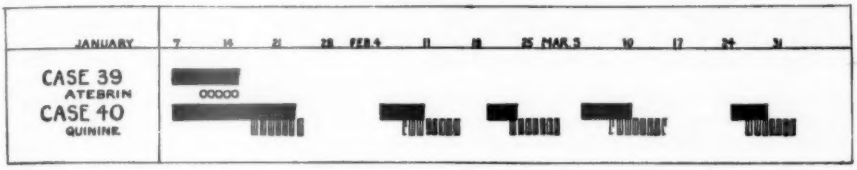
Atebrin 0·3 grm. daily (in tablets) at 10 a.m. for five days.

CASE 40.

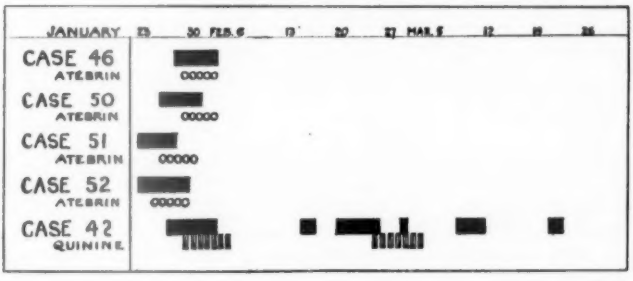
18.1.32.	At 10 a.m.	Quinine bihydrochloride	gr. x in solution orally.
	12 noon.	,, ,,	gr. v ,, ,, ,,
	5 p.m.	,, ,,	gr. x intravenously.
	11.30 p.m.	,, ,,	gr. x in solution orally.
19.1.32.	At 1.30 a.m.	,, ,,	gr. v ,, ,, ,,
	10.30 a.m.	,, ,,	gr. v ,, ,, ,,
	12 noon	,, ,,	gr. v ,, ,, ,,
	1 p.m.	,, ,,	gr. v ,, ,, ,,
	7 p.m.	,, ,,	gr. x ,, ,, ,,
20.1.32.	At 8 a.m.	,, ,,	gr. x ,, ,, ,,
	10 a.m.	,, ,,	gr. v ,, ,, ,,
	6.30 p.m.	,, ,,	gr. xv ,, ,,
21st to 24th inclusive.		gr. xv in solution twice daily.	

Blood examinations became negative as regards ring forms of the parasite in Case 39 (*atebrin*) on the third day after the commencement of treatment, and in Case 40 (quinine) on the fifth day.

The subsequent course of the cases is illustrated in the following diagram in which the black areas cover the periods of fever in the primary attack and recrudescences, the small circles indicate treatment with *atebrin* and the upright lines treatment with quinine, each line representing 10 gr.



We repeated this experiment with five patients, of whom four were treated in the primary attack with *atebrin* and one with quinine. All were patients who had never had malignant tertian malaria previously and all were infected with the Rome II strain on approximately the same dates by the bites of the same infected mosquitoes. The patient selected for quinine treatment of the primary attack was given gr. xxx daily for seven days, commencing on the second day of the attack. The administration on the first and third days of treatment was by separate doses of 5 and 10 gr.; on the other days administration was in two doses of 15 gr. (morning and evening). The other patients were given 0·3 grm. *atebrin* daily at 11.30 a.m. for five days, also commencing on the second day of the attack. The result of this experiment is shown in the following diagram:—



The following are some trials of the drug which we have made without at the same time treating a patient in the same category with quinine.

(1) *Rome III strain.* Case 38. Bitten by two mosquitoes from Rome on December 11, 1931, and by three on December 14. The primary attack began on the twelfth day after the second biting, with a temperature of 103·2° F., and ring forms of the parasite in the blood. Treatment with *atebrin*, 0·3 grm., was commenced on the evening of the third day after a febrile paroxysm with a rise to 104·4° and a parasite count of 400 per 100 fields of the microscope. The same dose of *atebrin* was given on the two following

days. After the last dose there was no further rise of temperature and no parasites were found in the blood. Period of observation since recovery three and a half months.

(2) *Rome II strain.*—The following three patients who were not cured by quinine treatment of their primary attacks were treated with *atebrin* in their first recrudescence:

Case 35. Bitten by one mosquito on 22.10.31. The primary attack began on 3.11.31. Quinine treatment, gr. xxx daily (in two doses) was given for five days, beginning on the second day of the attack. A recrudescence began on the seventh day after the end of the quinine course. Treatment with *atebrin* (0·3 grm. daily for five days) was given from the third day of the recrudescence. There was a quick recovery and no further recrudescence occurred. (Period of observation three months.)

Case 41. Bitten by one mosquito on 1.1.32. The primary attack began on 15.1.32. Quinine treatment, gr. xxx daily (in two doses), was given for seven days, beginning on the seventh day of the attack. A recrudescence began on the fourth day after the end of the quinine course. Treatment with *atebrin* was commenced next day and continued for five days. There was a quick recovery and no further recrudescence occurred. (Period of observation three months.)

Case 44. Bitten by mosquitoes on four occasions between January 5 and 10, 1932. Primary attack began 16.1.32. Quinine treatment, gr. xxx daily, for seven days, beginning on the third day of the attack. A recrudescence began on the ninth day after the end of the quinine course. Treatment with *atebrin* was commenced next day and continued for five days. There was a quick recovery and no further recrudescence occurred. (Period of observation three months.)

(3) Among the seventeen cases treated with *atebrin* one course of 0·3 gramme daily for five days failed to effect a permanent cure in the following case only:—

Case 43.—Bitten by fourteen infected mosquitoes (Rome II strain) on January 4, 1932, and again by five on the seventh and by four on the eighth. The primary attack began on the 16th January. Treatment with *atebrin* 0·3 gramme daily for five days was begun on the third day of the attack. The blood became negative on the seventh day of the attack (the last day of the atebrin course), but fever persisted until the eleventh day. A recrudescence with fever and parasites began ten days later. Treatment with *atebrin* as before was begun on the third day of this recrudescence and continued for seven (instead of for only five) days. There was a quick recovery and no further recrudescence occurred.

In this case the dose of infection was unusually large, for the patient was bitten on three separate occasions at a period when all the mosquitoes used carried sporozoites in the glands.

To sum up, with regard to the above successful results with *atebrin*, it may be said that they are important not on account of their number but because each experiment was arranged with a view to eliminate the errors in chemotherapeutic trials caused by the influences described in this Section under the heading "Treatment by quinine." We think that even a few trials of an antimalarial preparation conducted in this manner yield results which are more to be relied upon than a large number of trials made in circumstances where the only definite knowledge available about the cases is the specific name of the parasite found in the blood at the period of the trial, together with clinical details of the particular attack under treatment. It is evident that if the trials with *atebrin* had been made on cases infected with either of our Indian strains or perhaps with one of our West African strains, the successful results would have little significance, for as good results might be obtained with therapeutic doses of quinine. What is so noteworthy

about the results is that they were obtained on cases infected with strains of *P. falciparum* against which quinine was proved to be so ineffective that permanent cure by means of it could not be brought about.

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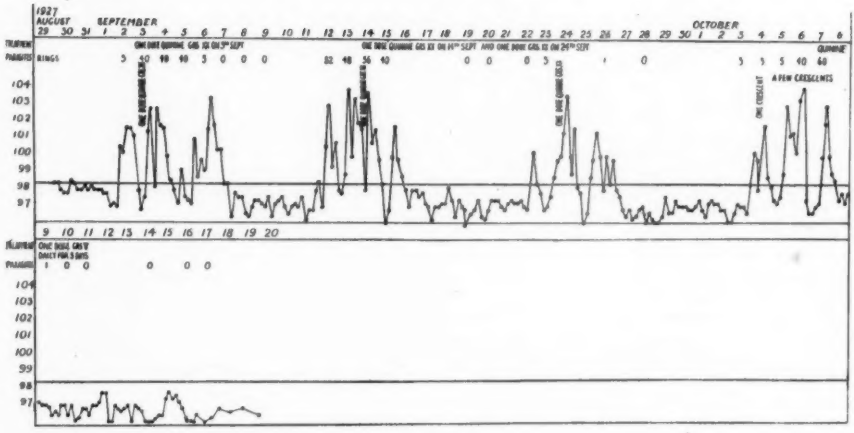
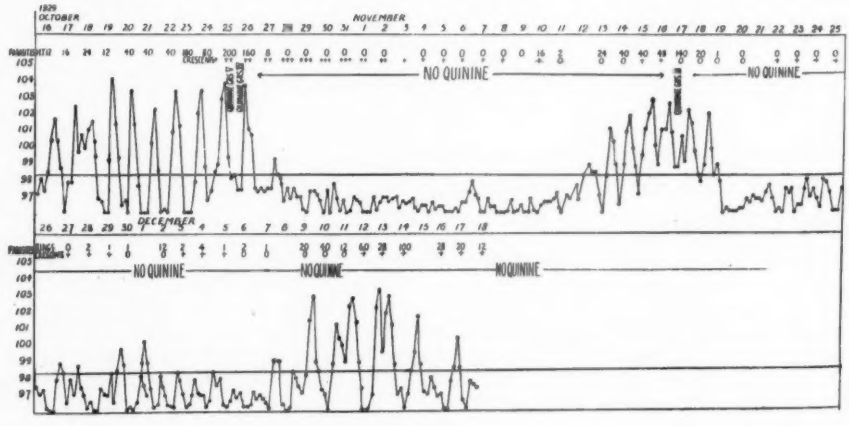
Dr. P. H. MANSON-BAHR said he had always believed that the subtertian parasite was on the whole more amenable to quinine treatment in the naturally acquired disease than the benign tertian, and that recrudescences such as one met with in this country, especially in West African cases, were more amenable to quinine therapy in smaller doses than the primary attack, and he agreed that it was only in the primary infections that an overwhelming parasitism and the development of pernicious symptoms were usually observed. It was just these heroic symptoms which demanded such heroic doses of quinine and here, the pure clinician and the experimental malariologist agreed. They would agree, too, that the life span of the malignant tertian parasite in the human body was considerably shorter than that of the benign. In this country after return from the tropics it was about one year. It was true that blackwater fever never accompanied a primary attack of subtertian malaria; it occurred only after repeated febrile doses of average severity; the development of blackwater fever really meant that the patient had harboured the parasite in his blood for several months and it was not a question of hyperparasitism producing methæmoglobinuria. The liability to blackwater fever persisted as long as the life of the malignant parasite. He had seen it develop after a residence of nine months in this country. He also agreed that overdoses of quinine were the main factor in producing blackwater fever and he could cite examples which made it difficult to escape this conclusion. With regard to quinine resistance, he had seen one case in which this appeared to be perfectly genuine: in a Dutchman, from Java, in whom oral, intramuscular intravenous quinine and plasmoquine had no effect whatever on the parasites. Although the patient was not ill and had no fever, the same observation had been made in Java and in Holland where he had also been treated. As to atebrin, he would like to have information of its untoward effects. He had read that this acridin-derivative caused patients to turn yellow.

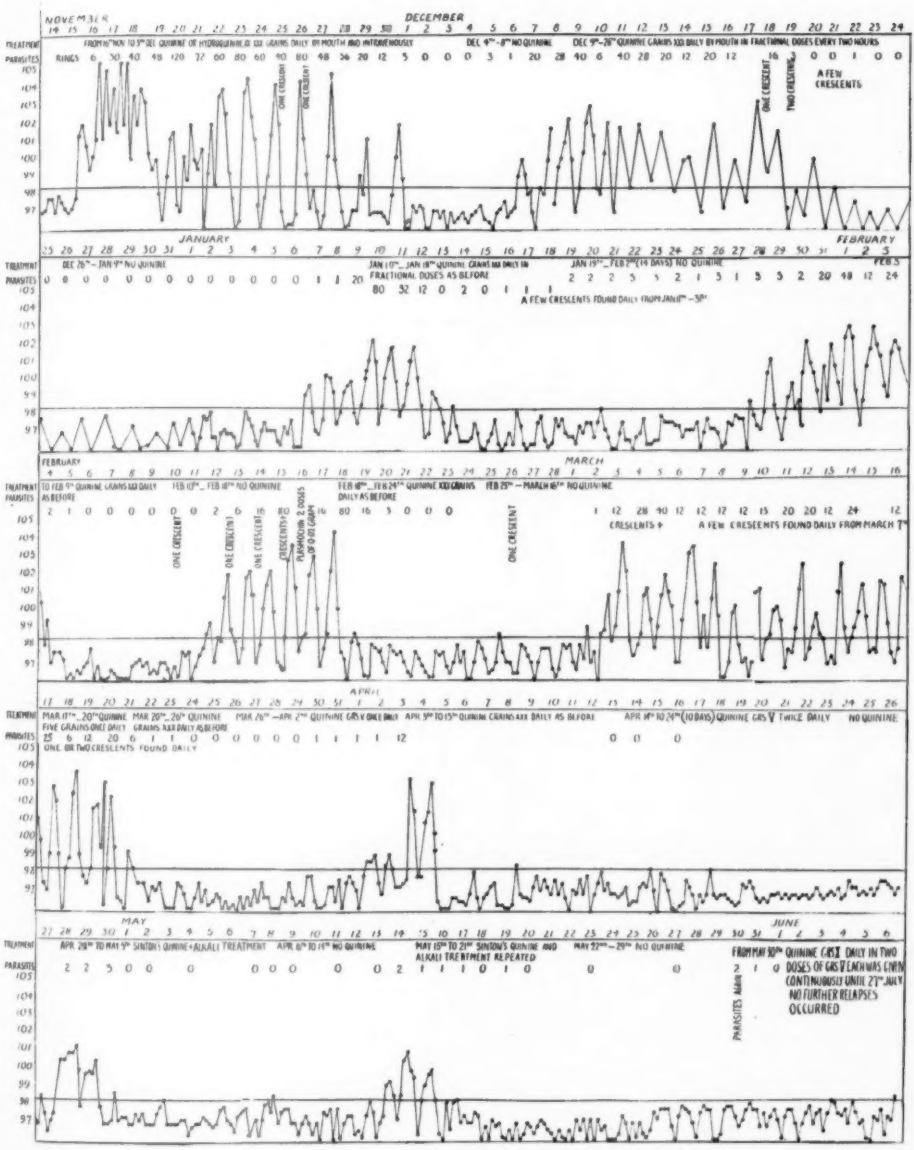
APPENDIX.



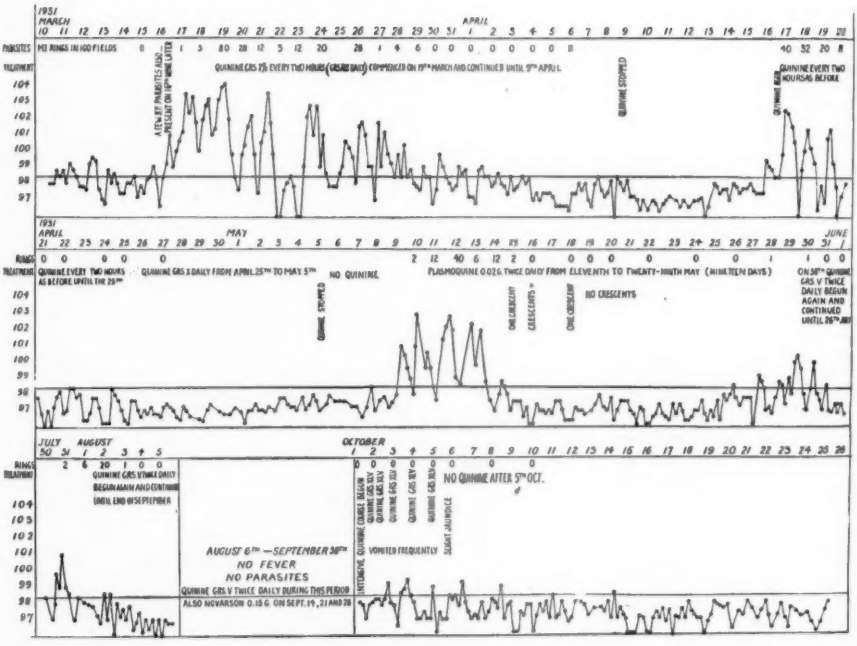
CASE 3.



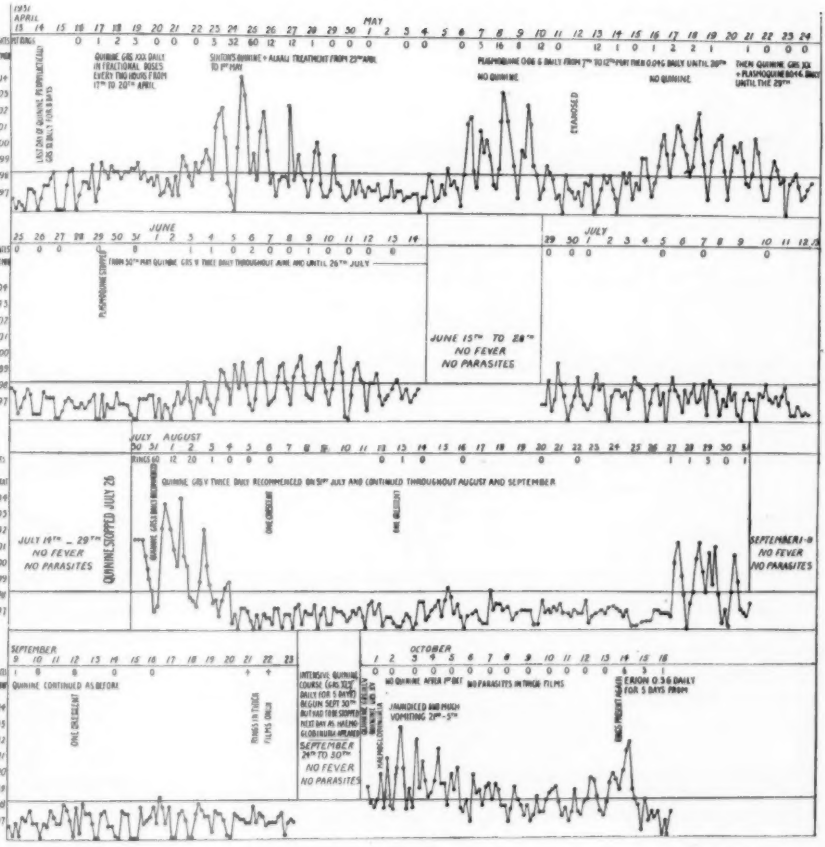
CASE 4.


NOVEMBER
DECEMBER
JANUARY
FEBRUARY
MARCH
APRIL
MAY
JUNE
TREATMENT
PARASITES
RINGS
FROM NOV 14TH TO 5TH DEC QUININE OR HYDROQUININE IX GRAINS DAILY BY MOUTH AND INTRAMUSCULY
DEC 9TH - 8TH NO QUININE
DEC 9TH - 26TH QUININE GRAINS XII DAILY BY MOUTH IN FRACTIONAL DOSES EVERY TWO HOURS
ONE CRESCENT
TWO CRESCENTS
A FEW CRESCENTS
DEC 26TH - JAN 9TH NO QUININE
JAN 10TH - JAN 18TH QUININE GRAINS IIII DAILY IN FRACTIONAL DOSES AS BEFORE
JAN 19TH - FEB 3RD (14 DAYS) NO QUININE
A FEW CRESCENTS FOUND DAILY FROM JAN 10TH - 30TH
TO FEB 5TH QUININE GRAINS IIII DAILY AS BEFORE
FEB 10TH - NO QUININE
FEB 18TH - FEB 24TH QUININE XII GRAINS DAILY AS BEFORE
FEB 25TH - MARCH 18TH NO QUININE
CRESCENTS +
A FEW CRESCENTS FOUND DAILY FROM MARCH 7TH
PLASMODIUM 2 DOSES OF 10 MIL GRAPH
MAR 17TH - 20TH QUININE FIVE GRAINS ONCE DAILY
MAR 20TH - 26TH QUININE GRAINS XXII DAILY AS BEFORE
MAR 26TH - APR 2ND QUININE GRS V ONCE DAILY
APR 3RD TO 13TH QUININE GRAINS XXII DAILY AS BEFORE
APR 14TH TO 24TH (10 DAYS) QUININE GRS V TWICE DAILY
NO QUININE
ONE OR TWO CRESCENTS FOUND DAILY
APR 28TH TO MAY 5TH SINTON'S QUININE + ALKALI TREATMENT
APR 6TH TO 14TH NO QUININE
MAY 15TH TO 21ST SINTON'S QUININE AND ALKALI TREATMENT REPEATED
MAY 22ND - 29TH NO QUININE
FROM MAY 30TH QUININE GRS I DAILY IN TWO DOSES OF GRS V EACH HRS GIVEN CONTINUOUSLY UNTIL 27TH JULY. NO FURTHER RELAPSES OCCURRED

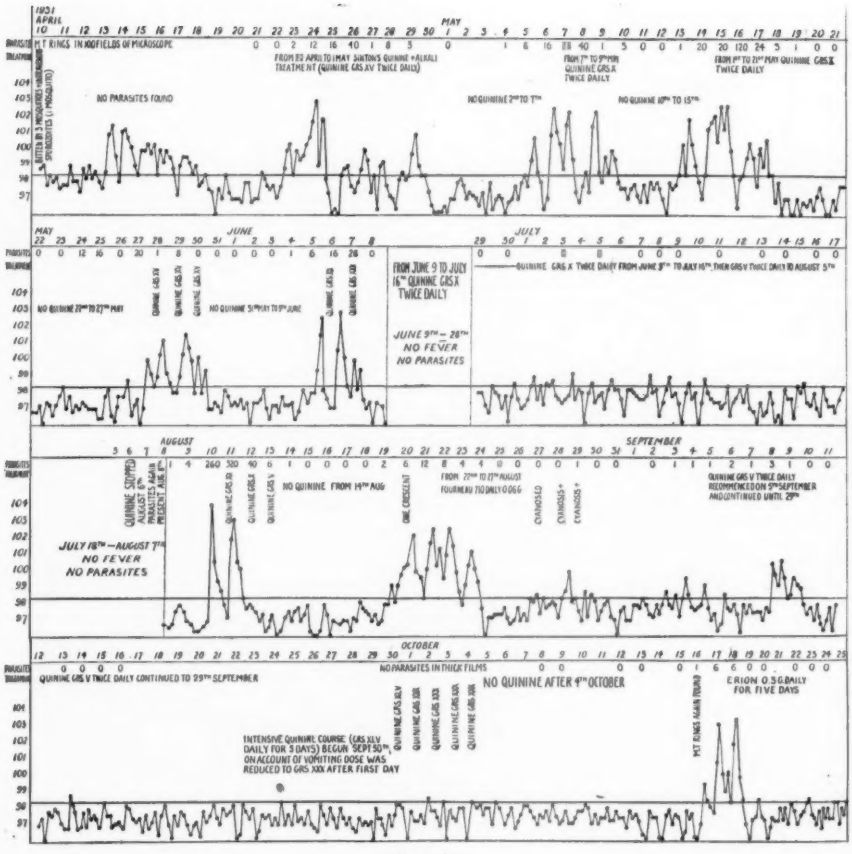
CASE 20.


1931
MARCH
APRIL
PARASITES
PER RINGS IN 100 FIELDS
TREATMENT
QUININE GRS 75 EVERY TWO HOURS (GRAND DAILY) COMMENCED ON 17TH MARCH AND CONTINUED UNTIL 9TH APRIL
A FEW RY PARASITES ALSO PRESENT ON 19TH WHICH LATER
QUININE STOPPED
QUININE AGAIN
QUININE EVERY TWO HOURS AS BEFORE
1931
APRIL
MAY
JUNE
RINGS
TREATMENT
QUININE EVERY TWO HOURS AS BEFORE UNTIL THE 25TH
QUININE GRS 3 DAILY FROM APRIL 25TH TO MAY 5TH
NO QUININE
PLASMOQUINE 0.026 TWICE DAILY FROM ELEVENTH TO TWENTY-NINTH MAY (NINETEEN DAYS)
QUININE STOPPED
ONE CRESCENTYS
ONE CRESCENTYS
NO CRESCENTYS
ON 30TH QUININE GRS V TWICE DAILY BEGUN AGAIN AND CONTINUED UNTIL 26TH JUNE
JULY
AUGUST
OCTOBER
RINGS
TREATMENT
QUININE GRS V TWICE DAILY BEGUN AGAIN AND CONTINUED UNTIL END OF SEPTEMBER
AUGUST 6TH — SEPTEMBER 30TH
NO FEVER
NO PARASITES
QUININE GRS V TWICE DAILY DURING THIS PERIOD
ALSO NOVARSON 0.15 G. ON SEPT. 19, 21 AND 28
INTOXICATION
QUININE GRS XV
QUININE GRS XIV
QUININE GRS XII
QUININE GRS X
QUININE GRS VIII
VOMITED FREQUENTLY
SLIGHT JAUNDICE
NO QUININE AFTER 5TH OCT.

CASE 27.


1931
APRIL
MAY
JUNE
JULY
AUGUST
SEPTEMBER
OCTOBER
QUININE GRS XXX DAILY IN FRACTIONAL DOSES EVERY TWO HOURS FROM 17TH TO 20TH APRIL
SINTON'S QUININE + ALKALI TREATMENT FROM 22ND APRIL TO 1ST MAY
PLASMOQUINE 0·06 G DAILY FROM 7TH TO 12TH
NO QUININE
NO QUININE.
THEN QUININE GRS XX + PLASMOQUINE 0·045 DAILY UNTIL THE 29TH
EXANGUINATED
PLASMOQUINE STOPPED
FROM 30TH MAY QUININE GRS V THREE DAILY THROUGHOUT JUNE AND UNTIL 26TH JULY
JUNE 15TH TO 28TH NO FEVER NO PARASITES
JULY 16TH – 29TH NO FEVER NO PARASITES
QUININE STOPPED JULY 25
QUININE GRS V THREE DAILY RECOMMENCED ON 31ST JULY AND CONTINUED THROUGHOUT AUGUST AND SEPTEMBER
SEPTEMBER 1–9 NO FEVER NO PARASITES
QUININE CONTINUED AS BEFORE
INTENSIVE QUININE COURSE (GRS XII) DAILY FOR 5 DAYS BEGUN SEPT 30TH BUT HAD TO BE STOPPED NEXT DAY AS HAVING GLOBULURIA APPARENTLY
SEPTEMBER 24TH TO 30TH NO FEVER NO PARASITES
JAUNDICED AND MUCH VOMITING 2ND–5TH
NO QUININE AFTER 1ST OCT
NO PARASITES IN THICK FILMS
ERGON 0·36 DAILY FOR 5 DAYS FROM

CASE 30.


1931
APRIL
MAY
M T RINGS IN 100 FIELDS OF MICROSCOPE
FROM 22 APRIL TO 1 MAY SINTONS QUININE + ALKALI TREATMENT (QUININE GRS XV TWICE DAILY)
FROM 7TH TO 9TH MAY QUININE GRS X TWICE DAILY
FROM 11TH TO 21ST MAY QUININE GRS X TWICE DAILY
NO PARASITES FOUND
NO QUININE 2ND TO 7TH
NO QUININE 10TH TO 15TH
JUNE
JULY
NO QUININE 22ND TO 27TH MAY
QUININE GRS XV
QUININE GRS XV
QUININE GRS XV
NO QUININE 5TH MAY TO 9TH JUNE
QUININE GRS X
QUININE GRS X
FROM JUNE 9 TO JULY 16TH QUININE GRS X TWICE DAILY
JUNE 9TH – 28TH NO FEVER NO PARASITES
QUININE GRS X TWICE DAILY FROM JUNE 3RD TO JULY 16TH, THEN GRS V TWICE DAILY TO AUGUST 5TH
AUGUST
SEPTEMBER
QUININE STOPPED AUGUST 6TH PARASITES AGAIN PRESENT AUG 7TH
JULY 18TH – AUGUST 7TH NO FEVER NO PARASITES
QUININE GRS X
QUININE GRS X
QUININE GRS V
NO QUININE FROM 14TH AUG
ONE CRESCENT
FROM 27TH TO 17TH AUGUST FOURNEAU 710 ONLY 0·066
CHINOSOL
CHINOSOL +
CHINOSOL +
QUININE GRS V TWICE DAILY RECOMMENCED ON 5TH SEPTEMBER AND CONTINUED UNTIL 29TH
OCTOBER
QUININE GRS V TWICE DAILY CONTINUED TO 29TH SEPTEMBER
NO PARASITES IN THICK FILMS
NO QUININE AFTER 4TH OCTOBER
ERION 0·3 G DAILY FOR FIVE DAYS
INTENSIVE QUININE COURSE (GRS XLV DAILY FOR 3 DAYS) BEGUN SEPT 30TH, ON ACCOUNT OF VOMITING DOSE WAS REDUCED TO GRS XXX AFTER FIRST DAY
QUININE GRS XLV
QUININE GRS XXX
QUININE GRS XXX
QUININE GRS XXX
M T RINGS AGAIN FOUND

CASE 31.

Section of Medicine.

President—Dr. H. Morley Fletcher.

Clinical Meeting held at the Royal Free Hospital, London, on Tuesday, March 22, 1932.

Abscess of Lung following Infarction, treated by Phrenic Evulsion.—D. C. Hare, C.B.E., M.D.

Mrs. E. M., aged 31, has suffered from hæmoptyses since early childhood. They occurred at the ages of 4 and 12 years and again with pregnancies at 21, 26 and 29 years. In January, 1929, she was admitted to hospital, being eight months pregnant and coughing up blood. The hæmoptysis recurred eight days later, the temperature rose and she came into labour. She shortly developed all the signs of lung abscess in the upper part of the right lower lobe. After eight weeks' fever and an unsuccessful attempt to establish a pneumothorax, phrenic evulsion was performed by Mr. Cecil Joll. The temperature fell immediately and recovery was uninterrupted. The patient had two small hæmoptyses in 1930 at six months' interval, but without any other symptoms or signs. There is no evidence of the cause of these hæmoptyses, no sign of tuberculosis, bronchiectasis or heart disease. Syphilis was probably acquired in or about 1924 and fully treated; the Wassermann reaction was negative in 1929. She had been in excellent health for the past year. She is the subject of lipodystrophy of the face.

Bilateral Polycystic Kidneys and Diabetes.—D. C. Hare, C.B.E., M.D.

Mrs. Emily M., aged 62. Patient has been under observation for four years. Symptoms began in 1928 with pain in the right loin and iliac fossa. Diabetes was found on admission in 1929 when exploratory operation for suspected carcinoma revealed the enlarged kidneys. At that time the blood-pressure was 175/105 and the blood-urea 36 mg. per cent. The blood-sugar before treatment was 400 mg. per cent. controlled by 55 units of insulin.

Recent examination shows that the kidneys have increased in size, the right now forms a large mass, but there are no symptoms of failure of renal functions. The blood-pressure is now 224/110. The fundus vessels show sclerosis and tortuosity; there are some petechial hæmorrhages on the right, which suggest hypertension and not diabetic or albuminuric changes. The diabetes is severe and difficult to control. There is a family history of diabetes in two sisters, but none of kidney disease.

Severe Colitis with Secondary Anæmia Cured by Intensive Liver Treatment.—D. C. Hare, C.B.E., M.D.

Miss E. B., aged 18. The onset of the illness was sudden, in September, 1930, with passage of blood in the stools and colicky pains and two or three stools daily. The condition persisted, but she continued her work till the beginning of December. There had been no previous attack.

On admission, December 12, 1930, the anæmia was severe; the spleen was not palpable. The stools contained a varying amount of blood and mucus, but no excess of pus; no specific infection could be detected. Sigmoidoscopy showed several patches of granulation tissue and one small ulcer at the recto-sigmoid junction. The fractional test-meal showed an acid secretion within normal limits. During the first two months, till mid-February, 1931, the general condition changed slightly for the worse; the evening temperature was always from 99° to 100° F. The anæmia improved temporarily after transfusion. Liver (4 oz. daily) was given for a short time at this stage, but appeared to increase the diarrhœa and was stopped. From mid-February to the end of March the symptoms increased, the stools were from six to twelve daily, with much blood, and were offensive; the evening temperature was up to 102° F. and the pulse to 125. The weight had fallen by 2 st. since the beginning of the illness. Massive œdema of the legs and trunk developed and the abdomen became greatly distended; later the œdema subsided and there was slight improvement in the appetite and general condition, but at the beginning of June the high temperature still continued and the anæmia remained practically unchanged. On June 7 liver extract equivalent to one and a half pounds daily was given.

The liver extract produced an alarming reaction for the first three days; the temperature rose to 103° F. and from ten to twelve stools were passed, but by the sixth day of treatment the temperature became normal for the first time for six months and never rose again above 99° F. The stools decreased to two daily and the weight rose by 4 lb. a week, or 2 st. in six weeks, by which time the blood picture was almost normal. There has been no relapse, though the patient was admitted with an attack of pneumonia during the winter.

Blood-counts.—November, 1930: Hb. 27%; R.B.C. 2·5 millions; C.I., 0·56; W.B.C. 7,500.

June 2, 1931 (before liver).—Hb. 24%; R.B.C. 1·25 millions; C.I., 0·9; W.B.C. 4,500.

July 28 (after 6 weeks liver).—Hb. 70%; R.B.C. 4·5 millions; C.I., 0·76; W.B.C. 13,000.

Osteitis Deformans in Mother and Daughter.—D. C. HARE, C.B.E., M.D.

The Mother. Mrs. C., aged 69, has noticed bowing of the right leg and of the left forearm for "at least" five years. She complains of very little disability, but has suffered from rheumatic pains. She is becoming deaf during the last year. Blood-pressure 160/80.

The bony changes appear to be limited to the right tibia and the left ulna. No change is detected by X-ray in the skull bones.

The Daughter. Miss A. C., aged 42. Swelling of the left tibia began five years ago; there is no history of injury, but at that time she had to stand all day and the leg was painful. The swelling has gradually increased, it is always hot and throbs a little, but she takes but small notice of it. No other bone appears to be affected. The Wassermann reaction is negative. The upper half of the tibia is enlarged and hot, the skin is unchanged. X-ray examination shows the bone to be expanded, streaked and rarefied, and the disease is considered to be osteitis deformans but other diagnoses have been suggested. The skiagram of the skull shows no change. In the mother the changes are those of sclerosis, though not very advanced; in the daughter the disease is in the early vascular stage with absorption but without much sclerosis.

The occurrence of the disease in father and son is referred to by Monchet.[1] No other reference to familial incidence has been traced. The mother, Mrs. C., states that her grandmother had a crooked arm.

[1] *Presse Méd.*, 1930, xxxviii, 1635.

"Essential" Hypertension.—D. C. HARE, C.B.E., M.D.

Miss G. D., aged 23, shop assistant.

Patient complains of mistiness of vision of recent origin and otherwise feels quite well except for occasional slight headaches in the morning. She had scarlet fever as a child.

On admission, the blood-pressure was systolic 230, diastolic 130; after a few days' rest in bed the reading was systolic 170, diastolic 100, but before discharge it had risen again, systolic 200, diastolic 138. The heart is slightly enlarged but otherwise normal. The renal functions appear to be but slightly impaired at the present time.

Urine.—Cloud of albumin, no casts. Urea concentration and water elimination tests:—Specimen A, after fluid restriction and 15 grm. urea: 385 c.c., specific gravity 1018, urea 2·5% (normal 3 to 5%). Specimen B, after 2 pints fluid: 275 c.c., specific gravity 1008, urea 1% (normal 0·3 to 0·8%).

Blood.—Urea 26 mg. %. Phosphates 3·04 mg. %. Wassermann and Kahn reactions negative.

The eyes show extreme changes in the fundus, the arteries are irregular and narrowed, in the right eye there are hæmorrhages and white exudates of cotton-wool appearance.

Chronic Acrocyanosis and Œdema of the Legs relieved by Non-Rubber Pressure Stockings.—D. C. HARE, C.B.E., M.D.

Miss M. S., aged 24. Employed in dairy work. The patient is a healthy young woman of the "blue" type, with slow peripheral circulation in both arms and legs. Before treatment the legs have been greatly swollen, cold and blue even in summer, and covered with chilblains in winter. She has felt great relief since wearing very tight surgical stockings; the swelling is controlled and the feet remain warm; she has had no chilblains on her feet during the present winter, in spite of standing all day on a cold cement floor in the dairy. During the same time she has had chilblains on her hands as in previous winters.

The stockings are made of thread and contain no rubber, and can be obtained from instrument makers and drapery stores.

Discussion.—Dr. F. PARKES WEBER said that the patient was an excellent example illustrating three different conditions, which often occurred separately in different patients, but were occasionally all three associated in the same patient: (1) Acrocyanosis, with red, turgid, sometimes clammy, hands; (2) a tendency to ordinary chilblains, especially on the hands; (3) the so-called "erythrocyanosis crurum" of girls and young (more rarely, older) women, a condition chiefly involving the lower part of the legs symmetrically, sometimes confused with erythema induratum (Bazin's disease) and often very troublesome in regard to treatment.

[Dr. HARE also demonstrated two cases of Lymphogranulomatosis Maligna which have been fully reported in the *Lancet*, 1932, i, 334.]

Cardio-Vascular Sclerosis Associated with Osteitis Deformans.—JENNER HOSKIN, M.D.

J. C., male, aged 65, carpenter.

Past history.—Syphilis when aged 22. First attended National Heart Hospital as out-patient on October 22, 1924, complaining of substernal pain on effort, considerable flatulence and loss of weight. Heart large, apex beat 4½ in. out; blowing mitral systolic murmur conducted outwards; aortic second sound accentuated; diastolic clear; peripheral vessels thickened. Blood-pressure 162/90. Pulse-rate 88, regular. Electrocardiogram physiological; Wassermann reaction negative; skiagrams showed no widening of aortic shadow.

Later history.—Has been free from anginal pain since October, 1926. Flatulence was diminished, but patient has had occasional cramp in the legs at night and numbness in the fingers at times, also occasional severe pain in the back after sitting. Kyphosis appeared and became more evident.

In October, 1927, he had a severe attack of shingles, affecting the eighth right dorsal root. Blood-pressure 185/80. Swelling of feet noted in February, 1928. Pains across back and down legs became more frequent in April, 1928. Signs of osteitis deformans were definite in January, 1929. Since that time the condition has become more marked. In April, 1931, swelling of shins with pitting noted. The blood-pressure has remained round about 180/90, and the heart condition has not changed materially. Osteitis deformans with considerable kyphosis is now present. An interesting feature is the marked tortuosity of the temporal vessels.

On the whole, the patient is keeping fairly well and has had no recurrence of angina. His walking, however, is rather difficult, and he has had to give up his work entirely.

Sino-Auricular Block.—JENNER HOSKIN, M.D.

J. D., male, aged 66. Wood-cutting machinist.

Past history.—Diphtheria at 15; scarlet fever at 20; influenza several times.

First attended National Heart Hospital as out-patient May 30, 1927, complaining of pain around heart in attacks and shortness of breath. Heart not enlarged; no bruits; rhythm irregular. Blood-pressure 160/100.

Electrocardiogram.—No preponderance; normal QRS and T complexes. Sino-auricular block with occasional ventricular escape.

Later history.—Has attended as an out-patient ever since. Was in-patient under Dr. Goodall from 15.11.1927 to 25.1.1928. Orthodiagram showed slight cardiac enlargement. Discharged very much better, but sino-auricular block unaffected by treatment.

Present condition.—Symptoms: Shortness of breath and occasional sharp pain under left breast. Heart and blood-pressure unchanged.

Electrocardiogram 22.12.1930.—Rate of normal beats, 85·7 (0·7 sec.); S.A. block beats, 46 (1·3 sec.); 31·6 (1·9 sec.).

Aortic Aneurysm in a Woman aged 31.—JENNER HOSKIN, M.D.

E. W., female, aged 31. Married.

History.—First attended as out-patient at Royal Free Hospital in April, 1928. Complained of pain over sternum radiating to back and down left arm, worse on exertion; also breathlessness.

Marital history.—One child, 8 years, healthy. No miscarriages.

On examination.—Heart, apex beat sixth space, $5\frac{3}{4}$ in. out; impulse heaving; no thrill; double mitral lesion. Loud, rough systolic and diastolic murmurs over base, and systolic thrill and bulging and pulsation over second left costal cartilage and in supra-clavicular notch. Blood-pressure: Right arm 140/50; left arm 130/45. Pulse, 80, regular. Brassy cough, tracheal tugging. Wassermann reaction negative.

May, 1928.—Skiagram: Heart much enlarged, mainly to left; aortic arch somewhat high and pulsating strongly; subclavian vessels also seen to pulsate vigorously. No aneurysm seen.

September 22, 1930, *to October* 16, 1930.—In-patient. Heart signs unchanged.

October, 1930.—X-ray report: Aneurysm of first part of arch of aorta.

Present history.—Still attending hospital as out-patient; complains of præcordial pain and headaches, occasional pain in back and legs and swelling of left ankle. Heart, in statu quo. Blood-pressure, 130/50.

Electrocardiogram (4.2.1932) shows a definite preponderance of the left ventricle, a regular rhythm of 76, T_I deeply inverted with negative S.T. interval, and T_{III} large and upright with positive S.T. interval.

Bilateral Sympathetic Paralysis following Thrombosis of Bulbar Vessels.—NEILL HOBHOUSE, M.D.

L. C., female, aged 66. In December, 1928, had a sudden attack of giddiness, with buzzing in both ears and failure of vision. Could not articulate clearly for some hours. Next day articulation became clearer, but she "rambled about things that happened long ago." For several days she was drowsy, and dropped things out of her left hand. When seen a week later there was severe vertigo, and she could only walk with support. Lateral nystagmus. Inco-ordination and asynergy in left arm. Still some dysarthria. There was complete bilateral paralysis of the cervical sympathetic. Wassermann reaction negative. Blood-pressure 150.

She made a good recovery, the only permanent residuum being the sympathetic paralysis.

Thrombosis of Posterior Inferior Cerebellar Artery, of Unknown Cause.—NEILL HOBHOUSE, M.D.

W. G. W., aged 59. In September, 1931, had a "stroke" and could not use the left arm or leg. Was unconscious for several days, then gradually improved. Was in an infirmary for four months.

Present condition.—Limitation of movement of left shoulder, due to secondary changes in the joint. Power otherwise fairly good. The signs in the central nervous system are: *Right*, complete sympathetic paralysis; pseudo-ptosis compensated by contraction of frontalis. Diminished sensation in trigeminal area, cornea almost anæsthetic. *Left*, inco-ordination and clumsiness, marked in arm, present to some extent in leg. Very little spasm, but extensor plantar response and evidence of slight pyramidal lesion. Sensation: still slight uncertainty to temperature. The condition appears to be residual now. Cerebrospinal fluid normal. Blood-pressure 145. Nothing has been found to account for the thrombosis.

Polyposis of the Stomach.—LIONEL E. C. NORBURY, F.R.C.S., and DANIEL T. DAVIES, M.D.

J. S., male, aged 58, has complained of indigestion for the past eight years. Blood noticed in stools during the past six years. Periodic attacks of pallor and shortness of breath alternated with periods of comparative well-being. Hæmatemesis occurred on one occasion—June, 1931. Symptoms of angina have also been observed when the patient was anæmic. In 1926 a laparotomy was performed—on account of the presence of a filling defect in the stomach on X-ray examination—but no actual disease was discovered. Clinical condition remained more or less stationary until June, 1931, when anæmia increased.

July, 1931.—At this time patient was very pale, the stools contained blood, the X-ray examination showed large filling defects in the stomach, and the gastric secretion an achlorhydria; hæmoglobin was 22%.

Measures to improve the blood were partially successful, but reactions following transfusion prevented more than two from being given. Iron and iron-containing foods were prescribed. The hæmoglobin rose to 52%, with the stools still containing blood, during a two-months' period.

September, 1931.—Operation performed (by L. E. C. N.). Large flat mass on lesser curve, with polypi arising from greater curve and posterior wall. Partial gastrectomy carried out. Patient made a good recovery, and a month later showed a hæmoglobin percentage of 65, and, two months later, of 70. Since the operation

the patient has enjoyed better health until recently when the stools were found to be black, the hæmoglobin had fallen to 58%, and symptoms of languor and dyspnœa returned.

The section of the polypi was examined by Professor G. Hadfield and reported as an adenomatous mass with malignant changes in the parent and larger mass on the lesser curve of the stomach.

The case exemplifies three of the characteristic features of polyposis of the stomach: (1) Repeated hæmorrhage, (2) malignant degeneration, (3) X-ray appearances.

Mediastinal Tumour.—L. S. T. BURRELL, M.D.

Male, aged 24 years.

History of febrile attack (T. 104° F.) with pain in chest and breathlessness, three weeks before admission. Increasing breathlessness and stridor since then. Swelling at base of neck noticed on day of admission. No previous history of illness.

Physical examination.—No orthopnœa. Inspiratory and expiratory stridor. Frequent cough. Mass of glands at base of neck on right side. Increase of paravertebral dullness. Percussion note flattened at right apex. Prolonged inspiratory and expiratory phases. No adventitious signs. D'Espine's sign positive.

X-ray examination (March 12, 1932).—Mass of glands in posterior mediastinum projecting to right side of spine at level of fifth thoracic vertebra. Aorta normal.

Sputum: No tubercle bacilli seen.

Blood-count.—R.B.C. 4,950,000; Hb. 90%; C.I. 0·81; W.B.C. 12,500; polymorphonuclear neutrophils 83·5%; polymorphonuclear basophils 5%; large lymphocytes 5%; small lymphocytes 5%; monocytes 6.

Rheumatic Carditis with Possible Traumatic Lesion of Aortic Valve.—L. S. T. BURRELL, M.D.

Robert B., aged 31. Until two years ago patient played football regularly and was an active swimmer. After being charged by another player on the football field he collapsed suddenly, with a sensation of something having given way in his chest. Since then he has become breathless on exertion and has suffered from attacks of precordial pain. No history of joint pains. Wassermann reaction negative.

Physical examination.—Pale, thin, breathless. Heart: Apex beat sixth space 5 in. from mid-line; forcible impulse. Systolic thrill at aortic base; systolic and diastolic murmurs at apex; loud, rough, systolic murmur in aortic area conducted upwards to neck; diastolic murmur heard down left border of sternum.

Electrocardiogram.—T waves inverted in all leads. Left ventricular preponderance.

The incident on the football field suggests the possibility of a traumatic lesion of the aortic valve.

Myasthenia Gravis.—L. S. T. BURRELL, M.D.

Miss P., aged 45. History of recurrent attacks of weakness of limbs and difficulty in speaking and swallowing for four years; attacks of diplopia and attacks of jaw-drop, with inability to swallow solid food, during this time.

Physical examination.—Mouth tends to fall open. Ptosis. Speech thick and slurring. Marked weakness of masseter muscles. Movements of palate less than normal. No wasting of muscles. No sensory loss. Knee and ankle reflexes difficult to obtain but present. Wassermann reaction negative. Kahn reaction negative.

Tuberculous Pyopneumothorax with recovery following Incision and Drainage of Pleura.—L. S. T. BURRELL, M.D.

William R., aged 41. History of pleurisy with effusion in January, 1928. Copious effusion with chest full to its limit, and the heart displaced to the right side. Eight pints of fluid were withdrawn at that time and replaced by air. Air replacement

was continued. The sputum and pleural fluids were positive for tubercle bacilli. After a course of sanocrysin his general condition improved, and he continued air refills at the Brompton Hospital.

In December, 1929, he was admitted to Brompton Hospital, febrile and with purulent fluid in the left chest. He improved with rest, and was transferred to Benenden Sanatorium. Paroxysmal cough with copious foul fluid sputum developed, suggesting a communication from a bronchus to the pyopneumothorax. On admission to hospital in April, 1929, there was a swinging pyrexia up to 102° F. nightly, and signs of a pyopneumothorax on the left side with copious foul sputum. The pus was withdrawn, and pleural washouts with methylene blue were given on three occasions. The chest wall was later incised and drained through a rib space. There was a persistent sinus following operation. Thoracoplasty was refused by the patient.

? Banti's Disease. Case for Diagnosis.—O. CAPPER-JOHNSON, B.M., B.Ch. (for T. JENNER HOSKIN, M.D.).

Mrs. Emily P., aged 38.

History.—For eighteen months the patient has been more easily fatigued on exertion and has been getting thinner than when in normal health. (She has lost about 1½ st.). Appetite has been poor; there has been no cough. She has noticed the tumour in her right side. No history of jaundice or any abdominal pain. Full investigations of the renal tract were made at St. Paul's Hospital; no abnormalities were discovered.

On examination.—Patient is rather pale and slightly puffy under the eyes. General nutrition fair. Abdomen.—On the right side there is a large tumour, extending below the umbilicus, with a vertical medial border with rounded edge; the posterior aspect is palpable in the flank. Spleen: enlarged to moderate extent. No enlarged lymphatic glands.

Investigations.—(1) Liver efficiency—function much impaired, as shown by lævulose test.

(2) Blood-count: R.B.C. 3,340,000; Hb. 50; C.I. 0·74; W.B.C. 6,250 (polymorphonuclear cells, 85%). (3) Reticulocytes, 1·6 per 100 R.B.C. (4) Platelets, 1 per 13·5 R.B.C.

(5) Twenty-four-hourly urine: Sp. gr. 1010. Granular and hyaline casts present. *B. coli* + +.

Section of Psychiatry.

President—Dr. BERNARD HART.

[*February* 9, 1932.]

The Principles of Psychiatric Classification.[1]

EDWARD GLOVER, M.D.

[AUTHOR'S ABSTRACT.]

THE psycho-analyst cannot postpone indefinitely the task of correlating psychiatric data with his own formulations on mental development, more particularly since material advances have been made in recent years in charting the earliest phases of ego-development. Psycho-analysts have no animus against existing classifications, but feel that their complexity tends to be in inverse ratio to the fundamental understanding achieved. The three main divisions are, moreover, closely interlocked. The conditions of an ideal classification were then considered, in particular the need for a system which will stimulate research. A purely descriptive method is not only inadequate but retrogressive. Nevertheless, it is temporarily of value if combined with other factors. It is also essential to relate the psychoses to mental phenomena as a whole. This involves correlation with the historical modifications of ego-structure. We must realize how psychotic infantile development actually is. A third factor is also necessary. This must be a specific (or almost specific) factor, in this case "loss of reality sense," i.e., disturbance of ego-object relationships.

As a preliminary to discussion of the developmental factor a description was given of psycho-analytic views of ego-structure, the relation of the ego to instinct and environment, and the rôle of anxiety as a signal system. Anxiety is the Alpha and guilt the Omega of human development: these reactions give rise to a series of instinct and ego modifications. Infantile instinct consists mainly of libidinal and aggressive tendencies, the former being divided chronologically into "primacies," viz., oral, anal and infantile genital. The author takes the view that any combination of libidinal and aggressive relations to an object gives rise in the infant to an ego-system or nucleus: also that the oral system contains many other nuclei apart from the main oral nucleus. These scattered formations converge about the age of two years, but already they are responsible for schizophrenic settings or fixations. The primal oral nucleus is probably independently responsible for melancholia. The later more organized nuclei representing anal and genital phases are associated with the neuroses. The earliest ego formations have not yet been fully investigated and in this field of research psycho-analysts and psychiatrists could advantageously co-operate. In particular, the "decomposition" products, stereotypies, etc., of schizophrenia require careful study and classification in order to establish the most primitive nuclear elements.

The primitive ego's relations to objects.—The fundamental point is that to begin with confusion exists as to ego-object boundaries. This is technically called "primary identification" of ego and object. Later this is followed by mechanisms of

[1] To be published in extenso in the *Journal of Mental Science*.

" projection " and " introjection," by which the ego, on the one hand, retains object characteristics and on the other projects painful ego characteristics on the object. These psychic mechanisms are based on early subjective experiences of instinct gratification and frustration. Expressed in psychiatric terms this primary confusion followed by the confusions due to introjection and projection, would correspond to a hallucinatory pan-psychosis, followed by an introjective psychosis of the schizophrenic and melancholiac type and a projective psychosis of the paranoid type.

In dealing with the fundamental mechanisms of schizophrenia, mixed states, melancholia and paranoia, oral impulse and frustration may be used as an illustration. The mixed states refer particularly to the phase when a rapid alternation of introjective and projective mechanisms exists as opposed to a temporary reliance either on introjective or on projective processes. This rapid alternation leads to a vicious circle in ego economy which can be broken in two ways: either by the action of repression or by establishing a more realistic and reassuring contact with reality. One of the advantages of introjection is that it helps to build up a controlling instance in the mind (viz., the super-ego) which plays its part in repression. One of the advantages of projection is that by attaching internal dangers to the external world of objects it puts a premium on more effective reality adaptation. When either process is exaggerated the way to psychotic reaction lies open. This applies not only to adults but to children; the child who does not come to terms with reality is in a true psychotic state of anxiety. The adult who has had difficulties at this early stage is liable to be plunged into a psychotic state when his safety systems (repression, etc.) break down. And they are liable to break down on occasions of severe instinct frustrations either external or internal. Prior to that breakdown an individual may be called a " potentially clinical psychotic." Reality sense, then, depends on being able to maintain contact with the objects in or through which post-infantile modified instincts are or can be gratified. Psychiatric standards, being partly social, are, however, not too severe. So long as the individual does not attempt to kill his introjected enemies by suicide or his projected enemies by homicide, society is not too exacting.

Adopting these criteria and applying them to the whole range of psychopathological phenomena, including various psychotic and neurotic character states and inhibitions, it is possible to arrange a rough parallel series. The arrangement is made in accordance with the amount of introjection and endo-psychic resolution of conflict on the one hand, and on the other with the amount of projection and exploitation of reality relations in the interests of resolution of conflict. Applying the reality test we are able to isolate the psychoses from the neuroses and neurotic character states. The most dramatic contrast at early levels is the contrast between melancholia and paranoia. Schizophrenia represents a more primitive level of introjection processes and is distinguished by the multiplicity of its primitive fixations to early ego-nuclei. The paraphrenias are in a sense alternating states, with mechanisms derived from both sides.

In considering the position of the neuroses special reference must be made to the anomalous position of the anxiety phobia, which has many projective elements.

Drug addiction is a true " borderline " state, having contributions from both psychotic and neurotic systems and at the same time preserving a fair amount of reality-relation for prolonged periods.

Future tendencies in classification.—It is suggested that later subdivisions may be made by reference to subsidiary instinctual mechanisms. It is also suggested, in regard to terminology, that a basic nomenclature should take cognizance either of the instincts involved together with the type of inhibiting mechanism or of the main divisions and subdivisions of psychic structure.

[*March* 8, 1932.]

Some Sources of Misunderstanding in Psychopathology.

By J. Ernest Nicole.

[Author's Abstract.]

In his presidential address at the beginning of this session, Dr. Bernard Hart[1] gave a survey of the modern fields of medical psychology and emphasized the possible good that might accrue from the employment of every kind of research or inquiry known to psychologists. He did not, however, have much to say concerning the confusion that might result from the simultaneous employment of these different lines of approach, each with its own theoretical background and its own terminology.

An attempt will be made to point out those pitfalls that are more in the nature of misunderstandings, due to the difficulty of reconciling the main theme of one psychological school with the central theme of another, and to the differences in terminology.

These difficulties are doubtless well known to the professional psychopathologist and technician, but there are many other workers who require some understanding of normal and abnormal psychology as a part—but only a part—of their mental equipment, such workers as anthropologists, ethnologists, sociologists, criminologists and educationists, to say nothing of general medical practitioners. Such an understanding will never be realized unless an effort is made to use terms in an unambiguous fashion, and until the writers of textbooks and manuals present psychology as a more united whole than they hitherto have done. A brief survey of the fields of psychology will be attempted in this paper, giving examples of some of these sources of confusion and misunderstanding, viewing these difficulties from the angle of the average general reader who does not aspire to become an advanced technician.

The psychology of a hundred years ago was almost entirely based upon the results of the study of consciousness by means of introspection, and it is the gradual introduction of newer methods that has led to a growing dissatisfaction with its findings and finally to the formation of the modern "schools." Perhaps the most direct offspring of the older psychologies is the "existential" school of Titchener, in which the central object of study and starting point of synthesis is *sensation*. The strength of the school owes a good deal to the adoption of a similar point of view by the neo-realist philosophers.

Another group of psychologists, having relinquished the position that psychology is the science of "mind," have conceived psychology as the science of "behaviour." Some of these have retained the concept of consciousness and admit the value of introspection, but the extremists have totally rejected both consciousness and introspection, and have founded the school of *Behaviourism*. This approach dates from the older animal psychologies and is based on Pavlov's findings concerning conditioned reflexes, so that all behaviour comes to be expressed in purely objective terms and regarded as the result of the conditioning and deconditioning of a few innate patterns of responses.

At the same time an attack was launched against the tendency for interpreting all higher mental processes as a mere integration of lower ones, such as the explanation of perception as an aggregate of sensations. This has led to the "Gestalt" school, the corner stone of which is the study of *perception*. This school insists that perception must be regarded as a whole, that in all perception there is an appreciation of "wholeness," a recognition of something belonging to the situation "as a whole," which is not recognizable in the simpler parts (sensations) of which other schools say perception is composed. Furthermore certain wholes, certain configurations or "sets" are so frequently found in perception, that they are actually

[1] *Proceedings*, 1931, xxv, 187 (Sect. Psych., 1).

sought for and imagined even in those situations which do not contain them, as when a certain type of curved line is perceived as an "incomplete circle" or another figure is recognized as a "truncated cone." Neither a circle nor a cone is actually seen, yet the perception is described in terms of imagined wholes or sets.

Finally another group of psychologists find their major theme in the interpretation of behaviour in terms of *purpose*. It is in this school that we find all psychology based on the assumption of certain fundamental trends, inherited urges, that are purposive and guide the animal towards a goal of successful adaptation and survival. As an example of such a "hormic" psychology may be mentioned McDougall's, with its elaborate instinct theories.

We have four main streams of thought, in which we find the principal emphasis laid on sensation, perception, reflexes, and purpose, respectively. Unless the student can find sure means of linking up with one another these several distinct schools he will not be able to avoid a considerable amount of confusion.

However, the "Gestalt" psychologists have shown how we make use of sets or configurations in making goals for ourselves, how our aims are formulated in terms of "wholes," and when they are thus stressing the function of our concepts of wholeness in our strivings, they are really only discussing purpose, the kind of purpose that looms so large in the hormic psychologies, although they do so from a different angle. We have here a meeting-ground of these two schools. Again, "Gestalt" psychology has shown the function of insight (as based on an appreciation of situations as a whole) in the solving of problems by animals, and in doing so has attempted to oppose the trial and error theory of the strict behaviourists. But there is a section of behaviourists, headed by Lashley, who are also casting doubt on the trial and error view by proving how an animal is often conditioned not so much for one particular stimulus as for one of several stimuli; in other words the animal's response often depends on the appreciation of the *difference* between stimuli: again an example of recognizing the "situation as a whole," a link between behaviourism and Gestalt. Further, some behaviourists recognize instinct as more than mere chain reflexes, as evincing purpose, thus standing midway between original behavourism and hormic psychology. Lastly, though many still deny consciousness and introspection, others maintain at least a non-committal attitude.

In connection with the word *purpose* there is the ever-present source of confusion in its double sense. From a mechanistic, causal point of view, purpose is merely the *result* of the events preceding it; but regarded teleologically, purpose is also a *cause* of the events leading up to its realization. It would therefore be of no little help if we used the adjective *purposive*—as Lloyd Morgan does—to denote purpose viewed from the causal, mechanistic angle, reserving the term *purposeful* for the final, teleological meaning, the meaning that implies the presence of that purpose in the mind of some agent or doer; in fact, purpose as a necessary part of a "dramatic" explanation of events.

McDougall's outlook on purpose is intimately bound up with his views on instinct, and here we find several difficulties productive of confusion. Thus the position of emotion in his scheme is not always clear, and many other writers regard emotion as distinct from instinct and possessed of a dynamic force of its own. Further, whereas McDougall describes many inherited tendencies, some of the experimental schools, for example, behaviourism, find very few innate patterns of response, at least in the unconditioned infant. But more important still is the fact that the accounts usually given of McDougall's instinct theories seem to imply that in absence of specific stimuli a given instinct will remain dormant. Now this is in direct opposition to those other "hormic" schools—the analytical—who insist that even in absence of stimuli an instinct leads to states of tension, of need, a condition of internal unrest that will urge the animal to *seek* those stimuli that will determine action of the desired kind. This has been expressed in neurological terms in that

"psychopathology of the autonomic" which is based on a synthesis of Watson, Pavlov, Freud, Jung and Adler, and which we owe to Kempf.

Misunderstandings may also arise from the fact that whereas McDougall's "instincts" are numerous the "analytical" ones are, at the most, three (ego, sex, and herd) and even to regard the latter as three *groups* of instincts does not help matters much. Lastly, the instincts of McDougall are classed in accordance with the immediate acts to which they prompt, whereas the three analytical urges are described in relation to the ultimate results that they achieve. In fact, the more one considers these broad analytical urges, the more does one realize that they are largely intelligent as well as instinctive, and that the very fact of their aiming for ultimate goals instead of immediate ones is due to the intelligent capacity for overcoming difficulties by means of thought and foresight. Although the exact relation between instinct and intelligence is debatable, one can yet reasonably suggest that the analytical instincts resemble far less what McDougall would call an instinct than those more complex trends that Shand terms *sentiments*. Indeed, these ego, sex, and herd tendencies of the analytical schools seem to correspond even more closely to what Morton Prince has called systems.

Another term, the meaning of which is seldom made clear by writers of text-books, is *intuition*. Every definition has been given it, from "supernatural cognition" to "instinctive knowledge." More recently it has been regarded by Dibblee as an extra-conscious epicritic and therefore cortical, function in the nature of unconscious thought, a view based largely on the work of Head and Rivers. Having mentioned Rivers we might add that in his work numerous examples of the confusing use of terms may be found. Thus, he employs the word *suggestion*, just as the French writers use *imitation*, to include the "suggestion," the "sympathy" and the "imitation" of McDougall. Matters are worse still in connection with *repression*, as Rivers applied it to what is now termed suppression, while using *suppression* to denote Freud's repression.

Repression may lead to *dissociation*; but it is not always clear that dissociation as understood by Freud or even, say, Morton Prince, is a dynamic process dependent on the expenditure of energy on the part of a "repressing force"; on the other hand, the dissociation described by Janet is explained by the latter as due to a diminution of energy, a weakening of the "synthesizing forces."

Another result of repression is the formation of a *complex*. This term is used to denote a repressed and buried system of emotions and thoughts (or "constellation," to use Jung's term), but one often finds the word employed so as to include conscious as well as unconscious constellations. In the latter case, complex becomes practically synonymous with sentiment, or even the "system" of Prince, and it is easy to appreciate the misunderstanding that may result from thus giving such an extended meaning to the word.

The theory of repression involves such concepts as *libido*, *ego*, *super-ego*, *id*, *fixation*, etc., and one cannot discuss these without entering a special technical field. The term *ego* was used in older philosophies with a mystical or transcendental meaning but it has come to be identified with the "self" of self-psychologists. And although the psycho-analytical use of the word is a very different one, it is not unusual for some of the less orthodox writers to evince a hybrid conception of the ego, one that superficially satisfies the demands of psycho-analysis, while at bottom being more in keeping with the tenets of self-psychology. Again the distinctions to be drawn between super-ego, ego-ideal and conscience, are often overlooked. The main difficulty in connection with *libido* is due to the unfortunate fact that Jung elected to apply it to all instinctive trends, instead of limiting it, as Freud does, to only a group of them.

Whether Jung's *collective unconscious* will ever be linked up with some enlarged conception of the psycho-analytic *id* is hard to say. Jung's use of the word *rational*

may also be misleading as it does not merely denote "reasoned" or "thought out"; it is used to describe all mental processes that are discriminating and involve a process of "evaluation," in contrast to that type of adaptation that is not discriminating, but empirical. The meaning of *introvert*, too, is at times evidently misunderstood, as one finds in the manuals of psychiatry a growing tendency for using introvert as another word for ego-centric or self-absorbed, the rôle of subjectivity and of the collective unconscious in the production of introvertion being lost sight of.

Many other examples of confusing terms could be discussed, such as *unconscious* and *co-conscious*, *conflict*, *regression*, *personality*, *character*, all of which are used in several different ways. Enough instances have been given to support a plea for a better consideration of the needs of the general student who aims at some understanding of several schools. The solution of these difficulties is not easy, but three suggestions can reasonably be made. Firstly, writers of textbooks should avoid attempting to convert the reader to one exclusive point of view. They should give a comprehensive and unbiased survey of the field, underlining the possible links between the various schools. Any fusion attempted between different points of view should be based on real understanding rather than on the confusion resulting from a lack of courage in facing terminological difficulties. Then, terms coined by a particular author should subsequently be used only in the sense intended by him. Lastly, any change in the delineation of a term should be in the direction of narrowing rather than enlarging it; as a result our terminologies would gain much in both clarity and conciseness.

[*April* 12, 1932.]

The Place of Psychology in the Medical Curriculum.

By David Forsyth, M.D., D.Sc.

The subject of this paper has often been discussed since it was raised by Dr. Bernard Hart in 1918[1]. It was dealt with by Sir George Newman in a memorandum to the Ministry of Health in 1923[2], and was reported on by a committee of the Royal Medico-Psychological Association in 1929[3]. Nevertheless, it can, I think, be profitably reconsidered at the present time.

Perhaps I should first explain how it is that one who is a general physician should discuss this topic. For many years psychology has been my chief interest. I recall my dissatisfaction as a student with the teaching given us, good though it was so far as it went, in that it failed to take into account the psychological aspect of clinical cases. After qualifying I had planned to enter the asylum service; I had been attracted by the adminstrative efficiency of asylums, but found myself more strongly repelled by the lack of scientific basis to the clinical work, and I felt that to live under these conditions would, psychologically speaking, mean intellectual death. Later I found myself on the staff of a teaching hospital, and in a few years more my disappointment with mental diseases was more than compensated by my coming upon psycho-analysis. This gave me at once the scientific satisfaction which I had failed to find in psychiatry, and set my chief interest permanently in the direction of psychology. For nearly twenty years now I have been regularly giving psycho-analytical teaching on neurotic and psycho-neurotic cases in my out-patient departments and wards, as well as several courses of lectures on psycho-analysis to students, the first of these being in 1919. During this time I have had ample opportunity to become familiar with the position of psychology in a teaching hospital, with the needs of both patients and students, and with the attitude of hospital physicians and

1 *Edin. Med. Journ.*, 1918, N.S., xxi, 213.
2 Memorandum on Recent Advances in Medical Education.
3 *Journ. of Ment. Sci.*, 1929, lxxv, 208.

surgeons in regard to it. I have ventured to give these particulars to show that I am perhaps specially favourably placed to indicate the situation in teaching and general hospitals to those who are better qualified than myself to present the psychiatric point of view.

(I) *The Present Curriculum* (*Undergraduate*).

The psychological training required of the medical student to-day is almost nothing: he must attend four-fifths of twelve systematic lectures on mental diseases, and twelve clinical demonstrations at a recognized institute for the insane. This part of the curriculum dates from 1893, when it was made compulsory by the General Medical Council. It has since remained unchanged, though the rest of a student's training has been revised, extended and modernized. Nevertheless, the date, 1893, marks the first recognition of psychiatry by general medicine. In this connection let me quote Dr. C. A. Mercier, president of the Medico-Psychological Association when the institution of a diploma in psychological medicine was under consideration and the suggestion of altering the undergraduate curriculum was negatived. "The amount of education in psychiatry which was given to the ordinary medical student could not very well be enlarged . . . . . What required to be given to the ordinary medical student who was going into general practice was such a knowledge of insanity that he would be enabled to recognize an insane person when he saw one, and so that he might know when it was advisable to call in a second opinion."[1] This then is still the extent of the knowledge of psychology required of a student—that he should be able to recognize an insane person when he sees one.

(II) *The Present Curriculum* (*Post-graduate*).

Though it is more than twenty years since steps were first taken in this country to institute a diploma in psychiatry, it is not easy to realize the position of this specialty before the present century. "The ghastly chaos of the madhouse"[2] existed even in the lifetime of the oldest among us, and the deep-rooted neglect both by the public and our profession of everything pertaining to mental disorders was common knowledge. This branch was kept in entire isolation from general medicine. Only slowly has its state been bettered, and even to-day the reconciliation is by no means complete. The substitution of medical for lay superintendents counted for more than anything else in establishing the present effective administration of mental hospitals. The foundation in 1841 of an Association of Asylum Medical Officers, which developed in 1865 into the Medico-Psychological Association of Great Britain and Ireland (to receive royal approval in 1925), together with the establishment in 1885 of the *Journal of Mental Science*, were the important milestones. The training of asylum medical officers was first taken up in 1892, when it was referred by the Association[3] to a Board of Education set up for this purpose, and three years later certificates of Competency in Psychological Medicine were granted after examination. These were competed for by few, and had little effect in raising the standard of efficiency. The next milestone was the establishment in 1895 of the first asylum laboratory—at Claybury, under Dr. F. W. Mott.

Most important of all was the institution of diplomas in psychological medicine. The credit for this is due to Dr. D. G. Thomson who in 1908 brought the matter before the Medico-Psychological Association. He urged in an able paper[4] that asylum work needed not only efficient administrators but proficient physicians, and that medical skill was the essential factor. Asylum experience produced pessimism

1 *Journ. Ment. Sci.*, 1908, liv, 556.
2 *Journ. Ment. Sci.*, 1908, liv, 550.
3 *Journ. Ment. Sci.*, 1892, xxxviii, 625.
4 *Journ. Ment. Sci.*, 1908, liv, 550.

as to prevention, but medical skill was needed in the treatment of recent and acute cases. Students were given only a smattering of knowledge, and mental disease was the only specialty in which no post-graduate training and special study were demanded. A medical superintendent in many instances was unqualified, even if he had time, to give or direct the training and teaching; only 5% of asylums possessed laboratories; dissatisfaction was widespread that no more scientific method of dealing with insanity was available, and that especially at its source. Reform depended essentially on a provision of post-graduate teaching. Dr. Thomson emphasized that only the recent or acute cases counted; the majority of cases in asylums were incurable, and nothing more could be done for them at present. In the discussion that followed, general support was given to the proposal.

The outcome of the discussion was a circular letter, signed by Dr. C. A. Mercier, president of the Association,[1] sent to all examining bodies in Great Britain and Ireland, representing "that the institution of a diploma would impose a high standard of acquirement in the officers of asylums, would stimulate the scientific study of insanity, and would have an effect in widening and deepening our knowledge of the subject, comparable with that effect produced in public health and tropical diseases, by the institution of diplomas in these subjects." It was further suggested that candidates must have been in the practice of a recognized institution for the insane for not less than twelve months, and that not less than one-third of the period of study must have been devoted to neurology.

Though the proposal was criticized as requiring too wide a knowledge several universities undertook to issue diplomas. The London College of Physicians, however, rested content with arranging in 1911 for an examination reserved for members of the College who might wish to have letters-testimonial added to their membership diploma. Apparently during the nine years in which this regulation was in force, the examination was taken by one candidate. In 1920, however, the College instituted a diploma in psychological medicine, influenced no doubt by the success of its recently instituted diplomas in public health and tropical diseases. Regulations were drawn up after conference with various teachers in the respective subjects, the diploma, be it noted, being instituted for and restricted to asylum medical officers.

(III) *Psychiatry and Psycho-analysis.*

No one can read the history of psychiatry in this country without being impressed by the continuous dissatisfaction of asylum medical officers with the isolation of their calling, an isolation scientific, professional and social. There was no special training in psychiatry, asylums were as a rule far from towns and research centres; asylum patients were for the most part beyond recovery, and no provision existed for their effective treatment. Scientific investigation and progress were lacking, and the problems of psychiatry were administrative rather than scientific. Moreover, the conditions of service in salary, promotion and opportunity of marriage were unattractive. As recently as 1915 Dr. C. H. Bond referred to psychiatry as the Cinderella of medicine.[2] Small wonder that there should always have been difficulty, even down to the present, in obtaining adequate medical staffs and in retaining them.

Psychiatry has mainly occupied itself with the humane reform of asylum administration, including the abolition of restraint, with establishing efficiency in the management and equipment of hospitals, and with improving the status and standard of professional skill of medical officers and nurses. The credit for these achievements, which in the course of half-a-century converted chaos into order, is largely due to the persistent efforts of the Medico-Psychological Association.

1 *Journ. Ment. Sci.*, 1910, lvi, 373.
2 *Journ. Ment. Sci.*, 1915, lxi, 1.

More recently, psychiatry has come to stress the importance, first recognized by Dr. Maudsley and Dr. Thomson,[1] of acute and borderline cases, in comparison with the advanced and incurable cases. As a result the idea of prevention has spread in recent years among psychiatrists whose efforts, too long obstructed by legal opinion, were largely responsible for placing the Mental Treatment Act on the statute book in 1930. This Act transforms the position of psychiatry in this country by legalizing the admission to mental hospitals without certification, by sanctioning treatment in voluntary hospitals without the intervention of judicial authority, and by permitting local authorities to undertake or contribute towards research.

One of the first beneficial effects of the Act has been the establishment of psychiatric clinics in connection with both mental and general hospitals. These clinics are the first new link in forty years between psychiatry and general medicine, and are endowed with unparalleled opportunities in the training of medical students, and therefore of the entire medical profession. No forethought should be spared to ensure their fulfilling what is required of them.

In contrast with these achievements, mainly administrative and legal, psychiatry still lags behind in scientific research and discovery. "Success," wrote Dr. J. R. Lord, in his "Clinical Study of Mental Disorders," 1926, "has not yet crowned its efforts to raise its efficiency to that of other branches of medicine." To-day mental patients, though their material conditions have been improved almost beyond knowledge, have hardly any better chance of recovery. Perhaps 33% are able to return to social life, though not as the result of treatment, but because of the natural tendency to recovery of some mental disorders. Indeed, the recovery-rate over many years has hardly varied.[2] That treatment is still only empirical is shown by the fact that the Board of Control[3] is at present furthering a scheme of treatment by ultra-violet rays and other light. Their express motive—viz., to make the patient and his relatives feel that everything possible is being done to ensure recovery—is eminently worthy, but scientifically the plan is a counsel of despair.

Altogether more hopeful, though from the point of view of prevention, is the decrease now apparent in the number of cases of insanity caused by syphilis and by encephalitis, and the striking decrease in the number of those from alcohol—an improvement still to show itself among the cases resulting from cerebral arterio-sclerosis.

Independent of psychiatry there has developed during recent years the theory and practice of psycho-analysis which, confining itself at first to neuroses and psycho-neuroses, has now for a good many years extended its investigations into the field of the psychoses. Apart from its claim to be a reliable instrument of scientific research, it has replaced the older static psychology by a dynamic psychology. Perhaps I shall best indicate its place in relation to psychiatry by quoting two writers, each a psychiatrist. In a paper, "The Clinical Study of Mental Disorders,"[4] Dr. J. R. Lord, referring to psycho-analysis, says :—

"The advent into British pyschiatry of dynamic psychiatry . . . . and the beginnings of a psychopathology, have carried with them a field of psychiatric research of a much wider character . . . . which help to illuminate the dark places in psychiatry."

Later, he says :—

"There can be no doubt as to the importance to clinical psychiatry of the study of child-life and development, i.e., genetic psychiatry . . . . The Freudian hypothesis of the auto-erotic, narcissistic, homosexual, objective-attachment stages of development, and their fixation or regression has come to stay, and is pregnant with meaning in the psychopathology of many cases of neuroses, psycho-neuroses and psychoses . . . . The psycho-analytical conceptions of Freud and their modifications by Adler, Jung and others constitute a . . . .

1 *Loc. cit.*
2 Board of Control—15th Annual Report, 1929 (for the year 1928).
3 *Ibid.*
4 *Journ. Ment. Sci.*, 1926, lxxii, 8.

school of dynamic psychology . . . . which is a distinct gain to psychiatry, especially . . . . to psychopathology . . . . The advent and growth of these new psychological views have given psychiatry a new vigour, ... and infused new hopes and aspirations for the future."

My second quotation is from the address delivered here last October by our President, Dr. Bernard Hart.[1] After showing that psychiatry has not yet passed to the level of a science, and that psychiatrists have manufactured disease entities instead of discovering them, he points out that even to-day in the backwaters of psychiatry attention is turned to anatomical, physiological and chemical processes, and says :—

"Freud introduced dynamic concepts, and advanced psychology to the level of a science. This is an epoch-making step which at once raises psychiatry to the level of other sciences. . . . It is only necessary that we should emphasize once more the momentous nature of the advance that Freud attempted, and its paramount significance in the history of psychological medicine."

Of psycho-analysis he says :—

"This will remain the first consistent attempt to apply to medicine a conceptual psychology along the lines which have proved so fertile in other branches of science, and has at last cast more light upon neurotic disorder than any other method. . . . The formulations of the psycho-analyst do enable us to interpret in psychological terms the conditions with which the psychiatrist has to deal. . . . The psychologist can claim that his method . . . has indubitably achieved greater success than any other so far as psycho-neuroses are concerned, and perhaps not much less success in the sphere of the psychoses."

If we accept these views—and they obtain my unqualified support—it follows that psycho-analysis not only has become the indispensable ally of psychiatry, but is the vitalizing, scientific stimulus which psychiatry has awaited these many years.

In any future scheme of training both psychiatry and psycho-analysis are indispensable. Neither alone is adequate. Psycho-analysis is of little or no help over a wide field in which psychiatry is usefully employed. It is of no value in connection with the many cases of general paralysis (6% of the total admissions to mental hospitals, and 11% of the male admissions). It has little bearing on the numerous other cases of syphilitic psychoses resulting from meningitis, cerebral endarteritis, tabes and gumma. Its utility is negligible in epidemic encephalitis, in senile psychoses resulting from cerebral arterio-sclerosis, and in toxic psychoses. In the large majority of cases of epileptic insanity as well as in all the host of cases of mental deficiency it cannot be helpfully applied. It offers no effective remedy or treatment for the great number of confirmed cases of paranoia, mania, melancholia and schizophrenia. Finally, it has no special place in the medical problems of the administration of mental hospitals. Yet the disorders just enumerated comprise almost all the cases in mental hospitals, and all those in institutions for mental deficiency. In this extensive practice the training must include not only psychiatry, but pathology, bio-chemistry, and neurology.

On the other hand, psychiatry restricts itself to advanced cases for which certification has been necessary, though recently it has shown increasing interest in *earlier* stages of these conditions—those with acute symptoms, or on the borderline. It has not concerned itself with minor mental ailments—neuroses and psycho-neuroses—with the psychology of childhood, with the *earliest* stages of the advanced diseases with which it has to deal, or with prevention. Yet all these are the special interests of psycho-analysis exclusively. Further, psycho-analysis has thrown light on many advanced psychiatric conditions. In the wide field of psycho-analysis special training in pathology, bio-chemistry or neurology is superfluous, but special knowledge is required of child-psychology (including infantile sexuality), folk-lore, mythology, anthropology and comparative religion, none of which is included in any curriculum for the diploma.

[1] *Proceedings*, 1931, xxv, 187 (Sect. Psych., 1).

(IV) *Psychological Cases in Teaching and General Hospitals.*

In contrast with the insignificant place of psychology in the curriculum, large numbers of the patients attending hospitals suffer from psychological disorders. In most cases the symptoms are early and mild. As a rule the patients complain of symptoms which might well indicate organic disease, and they are referred to the department dealing with that part of the body where the patient locates his chief neurotic symptom. Such cases are to be found in the neurological department, where the possibility of organic disease of the nervous system has to be excluded. But it is by no means only or even mainly to this department that they come. They are numerous in medical out-patient departments—often complaining of different symptoms on successive visits. Many of them attend the gynæcological department, where no local evidence of organic disease is discovered, others the genito-urinary department, complaining of bladder or kidney symptoms, or of symptoms referred to the male external genitals. They are in fact found in every out-patient department. Just how numerous they are in proportion to the organic cases is difficult to say; certainly they are a substantial minority, but they may be a substantial majority of the total cases. Psychologically, they are mostly cases of anxiety neurosis, conversion hysteria and hypochondria. Very rarely is a case found with mental symptoms calling for certification, and rarely with mental symptoms advanced enough to raise the borderline question.

From any of these out-patient departments, when there is doubt as to organic disease, the patients are usually admitted for further and often searching investigation, which is exclusively physical, and, as a rule, furnishes no sufficient evidence of organic disease. Any diagnosis attempted in terms of organic disease will often be prefixed by a "?". The treatment follows one of three lines:—

(1) The cases are treated as though organic. For example, on the medical side a patient complaining of epigastric pain will be treated on lines appropriate to gastric ulcer, thus perhaps convincing him that he is the subject of organic trouble, and intensifying his neurotic condition. In the surgical and other special departments operative treatment may be followed, if only exploratory, to make sure of the absence of serious organic trouble, or in the hope it may in some way bring relief.

(2) Patients are assured that they are without organic disease, but have weak hearts, delicate lungs, feeble digestions, and so on, according to their chief symptom. In most cases the medical opinion is accepted as infallible, and from then onward the patient's life is hampered by measures to lessen the strain on the supposed defective viscus. Some of these patients, finding their neurotic and hypochondriacal fears confirmed by medical authority, settle down to chronic invalidism.

(3) Yet another method is to insist that the troubles of these patients are imaginary, and to leave them without help. Nevertheless, neurotic symptoms are genuine, and may be more incapacitating than those of organic disease.

Even the important fact that no organic disease has been found, may not be explicitly made known to the patient, and practically never is anything said to let him know that his trouble is psychological, and requires to be treated psychologically. In fact this aspect of the case is usually never even thought of. Of the many cases of this kind which have passed under my notice, let me select three examples.

(i) A middle-aged man complaining of acute pain which he referred to the bladder, was admitted to a genito-urinary department. The case was systematically investigated with the help of every modern technical resource, and with uniformly negative results. He was told by the surgeon that nothing wrong had been found, and was sent home. Neither he nor his wife was given any hint of the possible psychological nature of his pain, or that his case might be amenable to psychological treatment. A few days later, the symptom persisting, he was examined psychologically and abundant evidence found on which to make the diagnosis of conversion hysteria.

(ii) A young married woman with pronounced neurotic symptoms had undergone eighteen operations, including two laparotomies, without the discovery of any organic disease; I was consulted when she had been admitted for a nineteenth operation.

(iii) A young woman complaining of bed-wetting was admitted into a surgical ward. A thorough physical investigation failed to disclose any organic cause. The operation for removal of the clitoris was performed. At no time was the psychological aspect of the case raised.

What has been said with regard to treatment in hospitals applies equally to general practice, and yet psychological cases are probably nowhere more numerous than in private practice. The practitioner, however, rarely allows himself to diagnose a neurotic condition, and even when he goes this far, his training does not enable him to deal with such cases, unless by suggesting rest cures and change of air. He is not at present acquainted even with the important rôle of the psychological transference in his dealings with all his patients, whatever their maladies.

This state of affairs could hardly be more unsatisfactory, and can be accounted for only by the entire lack of training and experience, alike of hospital staffs, general practitioners and students. When Professor G. M. Robertson recently deplored that "even the eminent consulting physician does not realize when he comes up against a mental case,"[1] we can only agree. It happens to be the eminent consultants of to-day who, as students 40 years ago, were the very first to enjoy the advantage of learning how to recognize an insane person at sight. Granted that more than this is not to be expected of them to-day, when their professional lives have been passed in activities out of touch with psychology, it is deplorable that the present generation of students should receive in this respect precisely the training that was considered sufficient for their professional great-grandfathers—a training which the Board of Control has recently characterized as "lamentably inadequate."[2] Equally in the post-graduate training for the diploma, though candidates are examined in psychiatry and neurology, no knowledge or experience is required of them in what Professor Robertson speaks of as the "very large field of minor mental ailments which cause great suffering and have been practically neglected in the past"[3]—a field which constitutes practically the entire psychological practice in general hospitals.

(V) *Changes needed in Post-graduate Training.*

It will hardly be disputed that changes in both undergraduate and post-graduate training are necessary. Indeed, Professor Robertson, after many years' experience of psychiatry, affirmed that "we have come to a critical point in the history of psychiatry in this country."[4] If this correctly summarizes the position to-day, it behoves us, before planning any changes, to form as clear a picture as possible of the situation as it will develop in the years ahead. The relative activities of psychiatry and psycho-analysis seem bound to be affected in the near future by three main considerations:—(1) The numerical proportions between mental hospital patients and patients suffering from minor mental ailments, (2) the effectiveness of treatment, (3) prevention.

(1) The latest official return gives the number of notified insane persons under care in England and Wales as 144,000[5]—rather less than 4 per 1,000 of the population (3·63 exactly). This number has shown no relative increase over a period of years. As to minor ailments, no figures are available, and no way of enumerating them can be suggested. At best we must rely on impressions, though

1 *Journ. Ment. Sci.*, 1931, 22.
2 Board of Control, 16th Annual Report, 1930 (for the year 1929).
3 *Loc. cit.*, 22.
4 *Loc. cit.*, 22.
5 The number of mental deficients is almost exactly 55,000.

there can be no question that the minor cases altogether outnumber the others. My own impression is that the persons suffering from psychological disabilities who could be helped medically, constitute not less than 50% of the population, but reducing this figure to one-half, we are still faced by a problem involving 250 per 1,000 of the population. In other words, for every one mental hospital case provision must be made for from 60 to 70 minor cases. Any scheme of training and treatment must therefore be mainly planned for the latter.

(2) *Effectiveness of treatment.*—The large proportion of minor cases are amenable to treatment, while the converse holds of advanced cases.

(3) *Prevention.*—This lies outside the scope of a mental hospital. To a limited extent it is involved in the work of clinics for the treatment of minor maladies in adults, but it is chiefly the concern of centres for children.

The situation to be envisaged in the near future would seem, therefore, to include: (1) very considerable extension of preventive mental hygiene and curative work among children, (2) considerable extension of curative work at clinics and treatment centres for minor adult cases, with (3) the mental hospitals for advanced and incurable cases. A psychological service so developed only mirrors the activities already tried out in general public health work, viz., child-welfare centres, hospitals for curative treatment, and Poor Law infirmaries for cases too advanced and chronic for admission to hospitals. Further, it may be anticipated that the more live activities of the service, together with research, will centre in the clinics for children, and to a less extent in those for adult treatment, while importance will shift from the mental hospitals.

No scheme can be realized without a supply of trained medical psychologists. This implies new arrangements for teaching, both undergraduate and post-graduate.

To take post-graduate training first. The present post-graduate curriculum varies but little as between one examining body and another, and we may take that of the Royal College of Physicians as fairly representative. The examination consists of two parts — Part I, to be taken any time after qualifying, comprises two papers, one in the anatomy and physiology of the nervous system, and one in psychology: Part II, to be taken after one year of special study, comprises also two papers, one in clinical and pathological neurology, and one in psychological medicine, including its legal relationships. Candidates for Part II are required to have attended for two months at a neurological hospital or out-patient department, and to have held a resident or whole-time appointment at an institution for mental diseases for six months. One-half of the examination is devoted to neurology: I have sometimes thought that psychiatry might have more confidently asserted its own importance against the claims of neurology.

This curriculum is the only officially recognized portal for those who may wish to specialize in the new developments in psychology. In this connection its shortcomings are evident. It includes no training or experience in psycho-analysis and its related subjects, no clinical experience in minor ailments, no acquaintance with the psychology of children, and it concerns itself hardly at all with prevention. It rests content with a mental hospital training only. To find a parallel we should have to suppose that the higher degrees in medicine and surgery were restricted to candidates with special experience of the chronic and advanced cases which are to be found only in Poor Law infirmaries. Moreover, though in the past a knowledge of psychiatry was, no doubt, to be acquired only by living and moving among great numbers of the insane, to-day we learn more by studying in detail a few patients whose sanity is as yet not in question. The psycho-analytical microscope has replaced the naked-eye methods of yesterday.

If there is substance in these criticisms, the matter is of some urgency now that psychiatry has at last the opportunity of establishing a real and living contact with general medicine. But by retaining the old-time training, is it helping to break down

the old-time prejudices? Is it not, instead, postponing the day when psychiatrists shall have acquired the scientific outlook, as well as comprehended the clinical experience which alone can bring them into harmony with their professional colleagues at teaching and general hospitals? Nowhere will this disability be more acutely felt than in child-clinics which are being staffed by psychiatrists untrained in child-psychology.

In our teaching hospitals we have a use for psychiatry, but it is minimal. Cases of insanity rarely present themselves, and these few, once recognized, are transferred to mental hospitals—just as chronic cases of organic disease are transferred to Poor Law infirmaries. Neither kind of case can have any claim to a place in a teaching hospital; nor can we require students to study any branch of medicine which is without a scientific basis. And is not this the reason why the curriculum has been unaltered since 1893? Perhaps, too, the absence of a scientific outlook explains the cleavage between psychiatry and general medicine which in this country, to quote Dr. Lord,[1] "reached a position of almost entire isolation."

The situation is otherwise with neurotic and psycho-neurotic cases, and now that clinics attached to teaching and general hospitals are being established, it is most important, if the scheme is not to be jeopardized at the outset, that those who will have the making or marring of their success should be trained and experienced in the kind of cases which form the very large part of hospital practice. It is often urged—by the Board of Control among others[2]—that these clinics should be in the charge of medical superintendents of neighbouring mental hospitals. This is all to the good in that it means that psychiatrists of standing and tested ability are to be appointed, but, as Dr. Thomson pointed out,[3] efficient administrators are not necessarily proficient physicians, and many medical superintendents are unqualified to undertake training and teaching responsibilities. In a teaching hospital the need is for a psychiatrist who has both the inclination and aptitude for teaching students, while in all hospitals, teaching and general, experience of mental hospital cases counts for little compared with experience of minor mental ailments. In this connection it may be pointed out that even the early, borderline cases which may now be legally treated in hospital clinics, are early only in contrast with the chronic cases in mental hospitals; compared with the minor mental cases in general hospitals, they are already advanced.

These observations have an added cogency in view of the difficulties which the work of the clinics may be expected to encounter from hospital staffs. The conservatism of hospital staffs is sometimes urged as an obstacle, though the staffs at any rate of teaching hospitals are progressively conservative—contact with the fresh minds of students accustoms them to reviewing their ideas and methods. At present the idea is still general among them that a mental case necessarily implies a troublesome, noisy patient who is probably suicidal. The need is to make clear to them exactly the kind of cases with which the clinics are concerned—cases of neuroses and psycho-neuroses which are already constantly coming under their notice in their own departments, are numerous, and are the most disappointing as they lend themselves not at all to physical methods of diagnosis and treatment. Once hospital staffs realize this, and that a clinic will take these cases off their hands altogether, they may be depended on to show the same readiness to accept the help of the clinic as they have the help of X-rays, clinical pathology, morbid histology and clinical chemistry. In this way psychiatry, isolated no longer, will take its legitimate place in general medicine, and come into close daily working contact with its various branches.

But this end cannot be gained with the present post-graduate training in psychiatry. Outstanding advance that it was twenty years ago, it needs modernizing

1 *Journ. Ment. Sci.*, 1926, lxxii, 8.
2 *17th Annual Report*, 1931 (for the year 1930).
3 *Loc. cit.*

and enlarging. The curriculum for the College diploma was already out of date at its inception in 1919-1920. Though I took no part in the preliminaries in connection with it, I knew something of what was going on, and the time is ripe to record a sidelight on the history of these preliminaries. I can vouch for its truth. The leading psychiatrists consulted in the matter undoubtedly desired to ensure a high standard in their specialty. At the same time most of them, as the contemporary medical journals show, regarded psycho-analysis with strong disfavour, and they were alarmed at the hold it seemed to be establishing in this country. In the event, the conditions of the diploma examination excluded all recognition of psycho-analysis, and ensured that the diploma should be granted only to candidates with the old-time asylum experience, and subject to the approval of examiners similarly trained. Shortly after these conditions had been informally agreed upon I met a distinguished psychiatrist who had taken a prominent part in framing them, and asked him about the new regulations. His reply was: "We've kept out psycho-analysis for the next generation." When it is remembered that the chief part in promoting the various diplomas was taken by Dr. C. A. Mercier, the leading opponent of psycho-analysis in this country, it is not surprising that the curriculum was behind the times from the start.

This short-sighted leadership has delayed the vitalizing of psychiatry and its reunion with scientific medicine for more than a decade. We need not, however, be too severe to-day when we recall that opposition to psycho-analysis at that time was widespread among leaders in other branches of medicine. Let me give another personal experience. In 1919 I wished to go to Vienna to Professor Freud—a visit deferred from 1914 by the war. As Austria was still technically an enemy country, permits to travel were issued only by the War Office, and so far no permit for a private civilian had been sanctioned. After some difficulty the War Office promised me a permit provided I had the support of a letter from the College of Physicians of which I was a Fellow. I wrote to the College, stating the purpose of my visit and asking for the support. In reply I was asked to call on the then President at his private house. This I did, only to learn that the support would not be forthcoming, and that on the sole ground that, as a psycho-analyst, I was "not a reputable person." To each of my arguments for half-an-hour I received the same reply. Happily I was able later to secure other official support. The War Office gave me a permit, and I went to Vienna.

The antagonism to psycho-analysis so general a decade or so ago, has lessened, but has by no means ceased Within my knowledge young medical men and women taking up psychiatry have been given to understand that their futures may be jeopardized by adherence to psycho-analysis. That the feeling in some quarters against psycho-analysis is even stronger than this would appear from an editorial article in the *Lancet*.[1] "In London to-day," it said, "few young men on the threshold of an academic career in medicine would dare to give open adherence to psycho-analytical principles, or even to investigate them in a scientific spirit." Does not this recall how in London Lister's discoveries were still rejected when they had been accepted the civilized world over?

It is evident that psycho-analysis still cannot reckon on being judged scientifically, even by some who claim to have the scientific mind. In so far as opposition comes from psychiatry itself, reform of post-graduate training, with all that can follow from it, is likely to be delayed, and the annual flow will continue of ingenuous young psychiatrists whose minds have been moulded to obsolescent shapes. Nevertheless, the necessary modifications of the curriculum are plain. Consider first the prominence at present accorded to neurology. Neurology has stood in an important relationship to psychiatry, but it is unserviceable in psycho-analysis.

[1] 1929, ii.

Long ago it assumed the rôle of foster-parent to the neuroses and psycho-neuroses, but the growth of the foster-children has never been helped by this dependence, and is now seriously impeded by it. It is interesting to inquire how this relationship grew up. Neurologists as a class do not seem to show special interest in any branch of psychology; when they foregather professionally, psychology is not a usual topic of discussion. Perhaps the foster-parentage dates from the time when cases of "nerves" began to attend neurological hospitals and departments, and the chief diagnostic problem was to distinguish them from cases of organic disease of the nervous system. This problem remains, but we now know that the same diagnostic problem exists in every specialty, and it probably reaches its largest dimensions in gynæcology. Consistently, therefore, if the diploma course is to include any non-psychological subject, candidates would be better required to have spent three months in the special study of gynæcology. Best of all, however, since psychological medicine is itself the largest and widest specialty in medicine and is able to stand without support, candidates should be examined in no subject outside psychology.

The most needed enlargement of the curriculum is to include experience of minor mental ailments. This necessitates a knowledge of psycho-analysis, which in its turn attaches outstanding importance to child psychology and preventive mental hygiene, as well as to experience of the earliest stages of mental disorders. As long ago as 1920, Dr. C. H. Bond[1] urged the inclusion both in the curriculum and in the examination of experience in the psycho-neuroses and psychotherapy, but progress in this direction has been slow, and as recently as 1930, Sir Maurice Craig,[2] speaking at the International Congress of Mental Hygiene at Washington, stated that "in England teaching with regard to minor mental disturbances is almost non-existing." A first step towards meeting this need has been recently taken at the Maudsley Hospital by Dr. E. Mapother, and at Bethlem Hospital by Dr. Porter Phillips, where the courses now include lectures on neuroses and psycho-neuroses. Although these lectures are few and no practical experience seems to be required, the development is significant.

(VI) *Changes needed in Undergraduate Training.*

Here the task is not, as with post-graduate training, to improve on past achievements, but to build from the foundations. Undergraduate instruction can hardly begin until a supply of trained teachers is forthcoming, but at present there is an almost complete lack of psychiatrists qualified for this purpose. We may perhaps profit by the position in the United States where, we are told by Dr. R. A. Noble,[3] the psychiatric buildings are wonderful and their equipment excellent, but the shortage of trained psychiatrists is a constant obstacle. In England we shall probably do better to remember that psychiatric clinics, if opened in teaching and general hospitals, cost little to organize and equip, and entail no building expenditure.

Every teaching hospital will require an out-patient clinic, and later, in-patient beds. Such a department will focus the psychological activities of both hospital and school. But students will benefit little from clinical material unless the ground has been prepared by systematic instruction. It will not suffice for this to be postponed until the final clinical years, any more than for medicine or surgery to be taught without a pre-existing knowledge of anatomy and physiology. The training in psychology should proceed alongside that in anatomy and physiology, to form the foundation for more advanced instruction in the clinical years. If attendance at the clinic for some months is made compulsory, as is now the case in other special departments, students will not only qualify with an adequate knowledge of psychology, but will pass into practice regarding psychology, like bacteriology or radiology, as an

1 *Journ. Ment. Sci.*, lxvi, 1920, 10.
2 *American Psychiatry*, by J. R. Lord, 1930, 16.
3 *Journ. Ment. Sci.*, 1931, 49.

integral part of medicine and clinical teachers will deal naturally and readily with the psychological aspects of their cases. This is surely altogether preferable to establishing psychopathic hospitals or independent schools of psychiatry.[1] And as by no means the least of the advantages of this incorporation in a teaching hospital a psychological department not only would be at the service of every other department, but would equally freely avail itself of the expert help of each other department as occasion arose. Thus established, it would constitute an important part of the Public Health Service.

Any suggested addition to medical studies usually raises the difficulty that the curriculum is already overcrowded. To this the reply is that the curriculum has never been immutable, but changes as the examining bodies are satisfied that the advances in medical science make it desirable. Adequate though the present curriculum is on the whole, it may be that some subjects—anatomy and physiology, for example—possessed greater importance in the past and now fill too large a place.

But if instruction in psychology is to be introduced, it is necessary for those who are specially interested to bring this about, to unite in submitting their case to the judgment of the leaders of our profession. If psychiatry has been slow in recognizing the value of psycho-analysis, psycho-analysis has been uninterested in many of the problems of psychiatry. Together they can effect much. The direction and extent of the next advance depends more on the psychiatrists than on the psycho-analysts, since all the influence in our academic councils rests with the psychiatrists. Much must also depend on the willingness of the neurologists to release their hold of a younger specialty which can get along best by itself. Circumstances have never been more favourable for coöperation, now that regard for the law, which has hampered psychiatry in the past is no longer a consideration, but only the interests of medicine.

Two words about the concern of the general public in this matter. It is worth raising an apparently trivial matter—whether our efforts to enlighten and help the public are not handicapped by use of the word "psychiatric" as applied to the clinics and other activities. "Psychiatry," "psychiatrist," "psychiatric," "psychiatrization" are words which look and sound queer to laymen. It may be wise to reconsider this nomenclature, especially if, as I have suggested, psychiatry will tend to become synonymous with mental hospital work.

To turn to a larger consideration. Very many of the public need psychological help on account of painful, handicapping mental ailments. They are increasingly aware of advances in psychology—perhaps more so than the medical profession. If they realize that the body of medical practitioners is entirely untrained to give this help, and if they find that our schools continue to turn out practitioners no less unqualified, may not our profession suffer a serious abatement of its influence by a substantial—perhaps the greater—part of preventive and remedial treatment passing away from it?

Energetic steps to amend the curriculum are surely needed. The Board of Control[2] is leading the way for all psychiatrists, and though the problem is larger than psychiatry alone can solve, psychiatric opinion must be satisfied before the next big advance in its history can be made. The last advance—the institution of the diploma—came on the initiative of Dr. Thomson,[3] and I will conclude with another quotation from his paper, leaving you to judge how far his words, uttered a quarter of a century ago, are prophetic to-day.

"We can no longer afford to rest on our oars and complacently gloat over the existing high-grade administration of our asylums, and we who profess to be specialists and leaders of opinion on matters connected with the insane should now be considering if the time has not come to take fresh stock of our position, to

1 *Journ. Ment. Sci.*, 1920, lxvi, 72.

2 *Board of Control 16th Annual Report*, 1930 (for the year 1929).

3 *Journ. Ment. Sci.*, 1908, liv, 550.

determine if our present methods of dealing with the insane and of teaching and training those who come after us are archaic or not. . . . . Familiarity and custom blind us to anomalies, so I would ask you to look at the matter afresh, and see if our present method of training the alienist is satisfactory."

Discussion.—Dr. WILLIAM BROWN said that he was in substantial agreement with almost all that Dr. David Forsyth had said. He would, however, emphasize the importance of the study of psychology by medical students at the pre-clinical stage, parallel to their study of anatomy and physiology. They would thus gain a sound grasp of fundamental psychological principles, and learn to think on psychological lines in a truly scientific way.

At this stage in their studies they tended to be keenly interested in psychological problems, as he had found in his classes in London and in Oxford, and the predominantly materialistic trend of their biological studies could then receive adequate compensation on the mental side, leading to a broader outlook and appreciation of the problems of personal and social relationships.

Dr. A. A. W. PETRIE said that in regard to the need of a different attitude among students, the medical profession and the general public, the Mental Hygiene Council were doing good work, and in time might induce the improved knowledge and better attitude already evident in the U.S.A. and Canada.

Not merely was the practitioner still in evidence who almost prided himself on his ignorance of psychiatry, but the attitude of the leaders of the profession might at times be more helpful. When more interest was taken in psychiatry by medical examiners the student would take a greater interest in the subject.

Present-day students were taking a much greater interest in psychology, the neuroses and other minor mental disturbances than formerly. There was an infinite amount of such material around students in their hospital work, and many of their cases, when they went into general practice, would be of this type.

The separation of the treatment of psychiatric patients from cases of general medicine had only occurred within the last 150 years, and the speaker hoped such separation would be lessened under the new Mental Treatment Act.

Dr. MILLAIS CULPIN said that the latter part of the nineteenth century was a period in medical history when psychological considerations were completely excluded from clinical medicine. The diagnosis of "functional nervous disorder" meant cessation of interest in the patient. There were likely to be serious difficulties in adding another subject to the curriculum, but a change of attitude from that in which the older generation had been educated would be beneficial and would necessitate very little addition to the student's load. Statistics were now being made available that showed the incidence of psychoneurotic disorders among some groups of the population, though many of them masqueraded under diagnoses of organic disease. In some groups over a half of all long sickness absenteeism was ascribed to such conditions as "nervous breakdown" or "cardiac overstrain." The seriousness of affairs was shown by the announcement in the medical press that a sort of psychological clinic was being established in London where people were to be treated by lay advisers. Doctors must accept their responsibilities to these patients or admit that they were beyond their sphere.

Section of Therapeutics and Pharmacology.

President—Dr. E. P. POULTON, F.R.C.P.

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Investigation and Treatment of Certain Cases of Disease of Muscles and Nerves.

By E. C. WARNER,[1] M.D., and A. C. HAMPSON,[2] M.D.

IN this paper are presented results obtained in studying the calcium and phosphate metabolism of a number of cases of disease of muscle and nerve. We shall first emphasize the results of the metabolic studies—for they are of statistical value whatever their significance otherwise—later we hope to be able to put before you certain results of treatment suggested by the biochemical studies. We realize that some of the diseases investigated, e.g., chorea, are self-limited; but some of the other groups studied are not in this position, as for instance progressive muscular atrophy in which a steady downhill course is the rule. So far as we are aware, there is no known treatment of any value for this condition and any new line of treatment likely to be of benefit should be carefully studied.

In many of the conditions under discussion there is a deficiency of calcium with an excess of phosphate in the cerebrospinal fluid. We do not, for a moment, imagine that these diseases are solely due to a calcium deficiency; we regard the question rather from the point of view of soil and seed. It may be that a large number of people have such deficiencies just as a large number of children have rickets, but that with such a soil a certain number, as a result of lowered resistance, become prone to infection on the one hand, or to a non-infective cellular degeneration on the other. There are a number of diseases which establish this well-known principle; for example, the underlying metabolic upset of calcium and phosphate metabolism associated with rickets, may result in a lowered resistance to infections such as produce gastro-enteritis or broncho-pneumonia or, alternatively, give rise to secondary changes of nerve cells and fibres, resulting in spasmophilia. We must realize that the same primary underlying cause manifests itself in many different ways in different people. Why this is so is unknown, but what could be more diverse than the way in which chronic lead poisoning may produce in one person wrist-drop, in another encephalopathy, in another arteriosclerosis, or in another a severe degree of secondary anæmia? In other words, there is considerable individual variation of response which must depend on individual variations, probably of a biochemical nature. To go further than this would be too speculative, but it is generally agreed that a common underlying cause such as an upset in calcium metabolism may be partly responsible for many different manifestations of disease depending on individual susceptibilities, subsequent infections, etc.

It may be of value to emphasize certain important physiological principles connected with calcium and phosphate metabolism.

First, with regard to calcium. Although most frequently studied, the total calcium content of the blood is not necessarily a measure of the *active* calcium.

[1] Ernest Hart Memorial Research Scholar, British Medical Association.

[2] Hilda and Ronald Poulton Research Fellow, Guy's Hospital.

Approximately 50% of the total calcium is present in an inactive form, probably combined with protein, and is incapable of passing through capillary or artificial membranes. The other 50% is in an active form, so-called diffusible calcium, and *is* capable of passing through capillary membranes, and this latter is the only portion capable of ionization. We may represent the average results on normal human blood thus :—

TABLE I.

Average total serum calcium	10·50	mgm. per cent. (9·6 to 11·5)
Average non-diffusible calcium	5·1	mgm. per cent.
Average diffusible calcium ...	5·4	mgm. per cent. (4·9 to 5·9)
Average ionic calcium	2·0	mgm. per cent.

Evidently the important point is the amount of active calcium, that is, of diffusible calcium and of ionic calcium. The total calcium is not necessarily in proportion to the diffusible portion. In pregnancy, Cantarow, Montgomery and Bolton [1] found considerable variations at different times in the same individuals.

TABLE II.

	Total calcium in serum		Diffusible calcium		Diffusible calcium. / Total calcium
Early pregnancy ...	10·61	...	5·08	...	48%
Late pregnancy ...	9·45	...	5·34	...	53%
First stage of labour	9·61	...	5·66	...	59%

The diffusible calcium can be separated by means of artificial membranes, but these methods are subject to criticism, owing to the length of time involved. Since the work of Marrack and Thacker [2], it is generally accepted that the best measure of the diffusible calcium of the blood is that present in the cerebrospinal fluid which, of course, contains a negligible amount of protein. From the point of view under discussion this is of additional value, because it represents the amount of calcium bathing the nerve cells and fibres. For this reason we shall here deal only with the calcium values of the cerebrospinal fluid. All our analyses have been made by Bainbridge and Trevan's method [3], and the average of at least three analyses has been taken. The normal values we found to lie between 4·9 and 5·9 mgm. per cent.

With reference to the phosphate in the blood and cerebrospinal fluid: The active form in the blood is the so-called inorganic phosphate, the value of which in normal individuals is about 3·0 mgm. of phosphorus per cent. It is doubtful whether all this inorganic phosphate is really active, as Snapper has found, if the estimation is made using other anticoagulents instead of the usual potassium oxalate, a value of the order of 1·4 mgm. per cent., and Hampson obtained the same figure working throughout at minus 5° C. This is the same value as we find in the cerebrospinal fluid, the normal range here being 1·2 to 1·4 mgm. per cent. It looks very much as if the cerebrospinal fluid phosphate may be a measure of the really active blood-phosphate. It is convenient to summarize here our normal figures in the cerebrospinal fluid for future reference.

TABLE III.—CEREBROSPINAL FLUID ANALYSES, NORMAL FIGURES.

Calcium average ...	5·4	mgm. per cent. (4·9 to 5·9)
Phosphate range ...	1·2 to 1·4	mgm. P per cent.

We should like to draw attention to the part that calcium plays in the normal metabolism of nerve cells and fibres. First, a lack of calcium gives rise to an increased excitability. A decrease of only 20% gives a maximum rise of excitability, and any increased excitability means a constant irritation with absence of adequate rest. Since Hilton wrote his treatise on "Rest and Pain" it has been realized how this lack of rest tends to promote degeneration. Secondly, we know that a lowered calcium content renders the cell membrane more permeable, and hence more liable to attack by toxins of various kinds. And thirdly, an excess of phosphate in the bathing fluids will depress the ionization of the calcium, and particularly is this true

in the case of the cerebrospinal fluid, which is about 0·2 pH more alkaline than blood.

Where we find a low calcium and a high phosphate present have we any method of correcting the balance? In the blood, the effect of an active parathyroid extract such as parathormone (Collip) is to raise the calcium and to lower the phosphate. In a recent case with a parathyroid tumour we obtained the results shown in Table IV. As soon as the overacting gland was removed the calcium rapidly fell and the phosphate rose until a condition of tetany resulted. Later these were adjusted nearly to normal values.

TABLE IV.

	Serum calcium in mgm. %	Plasma phosphorus (inorg.) mgm. %
Case of parathyroid tumour.		
Before operation	15·33 ...	2·2
Five days after operation	7·8 ...	3·9
Eleven months after operation ...	9·3 ...	3·6
Case of parathyroid tetany.		
Before parathormone	5·3 ...	5·8
After parathormone	9·3 ...	4·2
Normal values	9·6 to 11·5 ...	3·0

Case of tetany—the patient had an attack shortly after cerebrospinal fluid was taken.

Calcium in cerebrospinal fluid ...	4·36 mgm. % (normal 4·9 to 5·9)
Calcium in serum	9·82 mgm. % (normal 9·6 to 11·5)

The results obtained in a case of parathyroid tetany are also shown in Table IV. It is interesting to notice in this case that in addition to the spontaneous nerve phenomena, the patient complained of extreme weakness of muscles and great difficulty in walking across the room. One week after a course of parathormone injections she walked round Regent's Park. In the case of a patient who had an attack of tetany a few hours later we obtained the cerebrospinal fluid calcium value of 4·36 mgm. per cent. (It is worthy of notice in this last case that the blood-value was within normal limits, and was no guide to the low cerebrospinal fluid calcium.)

Cantarow [4] found that 2 c.c. of parathormone gave an average rise of 0·75 mgm. per cent. of calcium in the cerebrospinal fluid 4 to 6 hours later. So parathormone is evidently capable of acting in the manner required, as it raises the calcium in the blood and cerebrospinal fluid and simultaneously lowers their phosphate content. The only difficulty is that there is a considerable variability in the response of different individuals. This was first found by Collip in dogs; in the series in human beings by Cantarow just referred to, the maximum response varied from 0·1 to 1·8 mgm. per cent. This has certainly been our experience. Thus is one case of chorea we found:—

TABLE V.

E. H., aged 10. Chorea.	Cerebrospinal fluid calcium in mgm. %.
July 8	4·71 before treatment.
August 3	4·62 after 0·2 c.c. parathormone twice daily, no better
September 9	5·74 same dose of parathormone with 4 intra-musc. doses of calc. chlor. gr. 1. Free from chorea.

There is no evidence here of any effect of the parathormone, and in our experience some 20% of patients are completely resistant to it, whilst a certain number are partially resistant to it. Collip has found this lack of response may in part be overcome by giving additional soluble calcium salts, and Morgan and Garrison [5] found that an adequate amount of vitamin D or ultra-violet light was necessary. But even so, we feel sure there are other factors. A recent case of severe parenchymatous nephritis which Dr. Poulton allowed us to investigate gave an almost complete lack of response to the huge dose of 8 c.c. a day for fourteen days, and we shall, later, give other examples. The other great disadvantage of parathormone is its price. It costs nearly three shillings per c.c. which makes it extremely expensive to give over long periods to chronic cases.

TABLE VI.—CASES OF CHOREA SHOWING MINIMAL EXCITING CURRENT FOR THE "MOTOR-POINT" OF SUPINATOR LONGUS—IN MILLIAMPERES.

	No. of cases	Average current
Severe chorea	12	1·70
Mild chorea	14	2·09
Recovered chorea ...	24	2·56

We will now take some of the conditions studied and discuss the results. Results in chorea have already been published by one of us (E. C. W.) [6]. These children all show a rise in the electrical excitability of their nerves, as shown in Table VI [7]. Corresponding with these the blood-findings are within the normal limits, but there is a slight rise in the average calcium value as the chorea subsides. Much more significant are the cerebrospinal fluid figures.

TABLE VII.—CEREBROSPINAL FLUID CALCIUM VALUES IN CHOREA—MGM. %.

	No. of cases	Value of calcium
Severe cases	21	4·67 (4·36 to 4·93)
Mild cases	6	4·97 (4·57 to 5·60)
Recovered cases ...	8	5·15 (4·87 to 5·48)
Normal values ...	—	5·4 (4·9 to 5·9)

We have not so many results of phosphate values, but as the chorea subsides and the calcium figures rise, the phosphate values fall. This is shown in Table VIII.

TABLE VIII.—CASES OF CHOREA SHOWING RISE OF CALCIUM WITH FALL OF PHOSPHORUS IN CEREBROSPINAL FLUID.

Calcium	Phosphorus
4·33	1·76
4·52	1·77
4·81	1·73
5·31	1·58
5·43	1·52

Cases of chorea.

	Cerebrospinal fluid calcium	Cerebrospinal fluid phosphorus	Blood phosphatase
C. B.—Active chorea	4·93 ...	1·51 ...	0·294
D. J.—Active chorea	4·75 ...	1·64 ...	0·210
Recovered chorea	5·46 ...	?1·57 ...	0·152
W. W.—Active chorea	4·91 ...	1·60 ...	0·350
Recovered chorea	5·03 ...	1·21 ...	0·212

From this short series it appears as if the high cerebrospinal fluid phosphate may be related to a raised phosphatase in the blood.

From the point of view of treatment of chorea with parathormone, we have come to the conclusion that it is of some value in from 75% to 80% of cases. In some its value is very striking, whereas in others it appears to have no value at all. In the first twenty cases of chorea treated with it the average length of treatment till the complete cessation of chorea was four and a half weeks. The cases that respond are apparently those that have a simultaneous rise in the cerebrospinal fluid calcium, whereas the cases that fail do not show this rise. This is shown in two typical instances in Table IX. At the present price of parathormone it is questionable

TABLE IX.

	Cerebrospinal fluid calcium	
D. B., aged 7 ...	4·70 ...	active chorea
	5·23 ...	after fifteen days parathormone—recovery
E. H., aged 10 ...	4·71 ...	active chorea
	4·62 ...	after twenty-six days parathormone—no improvement
	5·74 ...	after sixty-five days parathormone and calc. chloride—recovered

whether it should be used as a routine, but it should certainly be tried in severe cases as it may prove effective. The most striking case was in a girl, aged 11, who

had such severe chorea that she rubbed out three sheets within the first twenty-four hours of admission to hospital, but whose chorea had quite gone in sixteen days and who left hospital within a month of admission. But in these dramatic cases there is a tendency to relapse if the parathormone is only used for a short period.

In contrast to cases of chorea, cases of progressive muscular atrophy show no tendency to intermissions and run a fairly steady downhill course. Our interest in these was stimulated by Captain Thomas's article in the *British Medical Journal* [8]. The author recorded two cases which definitely improved with calcium therapy. He injected "parathyroid extract" and gave calcium salts and cod-liver oil by mouth. Our investigations of cases of progressive muscular atrophy have in six cases out of seven shown a low cerebrospinal fluid calcium value, and in three out of five a high phosphate value. These are shown in Table X. We will give a short account of these cases.

TABLE X.—CEREBROSPINAL FLUID VALUES IN PROGRESSIVE MUSCULAR ATROPHY.

Case	Date	Calcium	Phosphorus
1	3.4.29	4·17	—
2	6.11.29	4·57	1·7
	7.5.30	—	1·58
	8.11.30	—	1·6
3	8.1.30	4·74	1·51
	15.7.30	—	1·60
4	4.3.30	4·44	1·71
5	6.2.31	5·46	—
6	4.9.31	4·54	1·26
	31.9.31	4·47	1·65
7	3.11.31	4·95	1·16
	27.1.32	—	1·05
Normal average		5·40	1·30

Case 1.—This patient was admitted to hospital 22 years ago with lead colic and wrist-drop, as a result of working as a painter. He made a complete recovery and remained well until eighteen months before his second admission. At this time he noticed weakness of the legs, and later he could not get out of bed, and if he fell he could not get up. On examination he had a "tapir lip" and extreme weakness and wasting of the arms and legs. After treatment, first with parathormone and later with doses of calcium lactate and radiostoleum, he has been able to walk much better. One day he came into the out-patient department saying he had walked fifteen miles the previous Sunday, doing it in stages. He is now earning his living again as a night-watchman, and the fibrillary tremors have disappeared.

This case certainly appears to be one of those described by Collier as following lead poisoning. As a result of the work of Aub and Hunter, cases of lead poisonng are being treated with calcium salts which may account for the definite progress made in this case.

Case 2.—This patient's symptoms began in May, 1929, and by November, 1929, whilst under treatment elsewhere, he rapidly and progressively went downhill, so that he was unable to get out of bed by himself or to feed himself, and could only walk a few yards with assistance. The condition had begun in his hands and soon affected his feet, and he had difficulty with speech and with swallowing. After the first course of treatment with parathormone he showed some improvement and he could walk into the out-patient room without assistance. At present his condition is much the same as when he was first seen, so that the atrophy seems to have been arrested. He can walk and may stumble, and if he falls he cannot get up unaided. His phosphate has fallen to 1·6 mgm. Treatment has consisted in ½ c.c. doses of parathormone twice daily for two months in the first instance and since then for seven days each month, with radiostoleum for the rest of the month. He has had calcium gluconate by mouth throughout.

Case 3.—A stubborn and difficult patient who will not carry out treatment at home. When first seen he could not walk, and was given parathormone injections together with massage and exercises which set him on his feet. He was taught to give himself injections at home but failed to do so. Six months later he was as bad as ever and injections of distilled water made no impression. Again, he made good progress with parathormone injections together with massage and exercises but he has since been lost sight of.

Case 4.—The patient had had progressive muscular atrophy beginning in the legs, four months before she was first seen. This was a rapidly progressive case in which parathormone made no difference at all. The patient rapidly went downhill with a progressive condition and died some ten months after its onset.

Case 5.—This patient's trouble began two months before he was first seen in January, 1931. He had considerable wasting and weakness of the right hand and slight wasting of the left hand. He made no complaint of his legs but fibrillary twitchings were seen in all the muscles of the arms and slightly in those of the legs. This condition was arrested with twice daily injections of parathormone and the patient was most eloquent of the way this "built him up." He stopped the treatment in June, 1931, and began work as a gardener, using a strap to fix the mower to his wrist. By September he had gone downhill rapidly again. Since then he has had injections seven days each month with calcium gluconate and radiostoleum as in Case 2, and for the past month has had parathormone the whole time. When he has been having no parathormone he has gone downhill fairly rapidly but has pulled up again with the injections. He is now in much the same condition as he was one year ago, except that his right hand is not so strong; here again, the condition seems to have been arrested.

Case 6.—In this case the atrophy had begun two months before the patient was admitted in September, 1931. It was rapid and progressive, and although he had treatment with parathormone, calcium gluconate, radiostoleum and ultra-violet light continually, he made no improvement at all and died in December, 1931. The paralysis actually extended from the legs to the arms and trunk while he was under treatment and the fibrillary twitchings were well marked throughout. We can see from the values obtained that in spite of treatment the calcium in the cerebrospinal fluid fell still further and the phosphate rose. The patient certainly appeared to be completely resistant to the effects of parathormone, and of calcium therapy.

Case 7.—This is an early case first seen in October, 1931. The patient drove a hospital ambulance and complained that he could not grip the driving wheel properly. He has had daily injections since then, and though in such a short time it is difficult to assess the effects of treatment, he has returned to his work and acts as a spare man, taking control and driving for short distances.

To sum up these cases—Cases 4 and 6 made no progress with treatment and the patients have since died; in one of these cases we know that parathormone exercised no effect on the cerebrospinal fluid. Cases 1, 2, and 5 have remained under treatment; the fibrillary tremors have largely disappeared, and in place of a steady downward course they have remained stationary or actually improved to the extent that in Cases 1 and 5 the patients are earning their own living. Case 3 improved when under treatment but the patient has ceased attendance and has been lost sight of. Case 7 is in too early a stage to assess as yet but so far the result has been satisfactory.

TABLE XI.—CEREBROSPINAL FLUID VALUES IN WERDNIG-HOFFMANN'S ATROPHY.

	Date	Calcium	Phosphorus	
Case 1 ...	— ...	4·34 ...	1·75 ...	Died
,, 2 ...	— ...	— ...	1·72 ...	Died
,, 3 ...	12.8.31 ...	4·64 ...	1·60	
	15.11.31 ...	4·91 ...	1·43	

We have investigated three cases of Werdnig-Hoffmann's muscular atrophy in babies. The results are shown in Table XI. The first two patients died three and ten days after admission, with intercurrent infections, before treatment was started, but the third has done very well. The only treatment she has received has been 2-minim doses of parathormone injected twice daily with calcium salts and radiostoleum by mouth. When first seen at the age of 17 months she had the typical well-covered face and wasted limbs, her biceps being about the size of a pencil. She could not move her legs and could scarcely move her arms. Now she can walk round her cot, her muscles are much better developed, presumably by hypertrophy of the remaining muscle fibres, and although her diet has not been changed, her gain in weight is very

gratifying. It is recorded in Table XII. Her subsequent cerebrospinal fluid has shown definite improvement also (Table XI). For the past two months the parathormone has been omitted, but the calcium gluconate and radiostoleum are being continued.

TABLE XII.—SHOWING THE WEIGHTS OF PATIENT SUFFERING FROM WERDNIG-HOFFMANN'S ATROPHY BEFORE AND AFTER TREATMENT.

		Grammes
April, 1931	...	9,070, the highest weight attained before loss began. Aged 13 months
August, 1931	...	6,400 on admission
,,	...	6,200 six days later, immediately before parathormone was started
November, 1931	...	7,500
February, 1932	...	8,750 (approx.)

We have investigated a certain number of cases of muscular dystrophy. Three of the pseudo-hypertrophic type have given essentially normal cerebrospinal fluid findings. Table XIII.—With the exception of Case 3 these patients have not had treatment. This particular patient was most anxious to try injections and is reported to have made slight progress. We have not been able to follow him as he lives on the coast. These cases are in contrast to a case of facio-scapulo-humeral dystrophy.

TABLE XIII.—CEREBROSPINAL FLUID VALUES IN CASES OF MUSCULAR DYSTROPHY.

	Date	Calcium	Phosphorus	Type
Case 1 ...	— ...	4·97 ...	— ...	Pseudo-hypertrophic
,, 2 ...	— ...	5·05 ...	1·38 ...	,,
,, 3 ...	— ...	5·66 ...	1·42 ...	,,
,, 4 ...	10.6.31 ...	4·42 ...	1·20 ...	Facio-scapulo-humeral
	12.11.31 ...	— ...	1·03	

Case 4.—This patient, aged 16, when first seen in June, 1931, had a four years' history of wasting and weakness, chiefly involving the shoulder-girdle—slightly the pelvic-girdle—and he had a tapir lip. At first he was unable to support any weight in either hand. He has had contractures of the right elbow gradually straightened out, and he can now support a 6-lb. weight in the outstretched hand on both sides. The muscles are firmer and better developed. It is difficult to say how much of his progress has been due to the massage and exercises associated with overcoming the contractures of the arms, but it is difficult to imagine that he would have improved so much had he not received parathormone for ten days in each month.

The remaining cases are due to cerebral lesions of various kinds. Two cases of post-encephalitis lethargica and three cases of disseminated sclerosis have given normal results in the cerebrospinal fluid (Table XIV). One of the latter was given parathormone and calcium salts and actually had an exacerbation whilst on this treatment, but two cases of post-vaccinal encephalitis in the acute stages gave rather low calcium values and very high phosphate values; both these cases received treatment with parathormone and did quite well.

TABLE XIV.—CEREBROSPINAL FLUID VALUES.

Case	Date	Calcium	Phosphorus	
1 ...	— ...	5·49 ...	1·1 ...	Post-encephalitis lethargica
2 ...	— ...	5·24 ...	1·2 ...	,, ,,
3 ...	— ...	4·90 ...	— ...	Disseminated sclerosis
4 ...	— ...	— ...	1·12 ...	,, ,,
5 ...	— ...	5·36 ...	1·47 ...	,, ,,
6 ...	— ...	4·94 ...	2·3 ...	Post-vaccinal encephalitis
7 ...	— ...	4·7 ...	2·5 ...	,, ,,
H. C. ...	6.11.29 ...	4·44 ...	2·7 ...	Schilder's encephalitis
	9.3.30 ...	4·86 ...	1·2	

The most interesting and striking case of encephalitis, however, was a case diagnosed as probably one of Schilder's disease.

H. C.—The patient was a boy aged 9, admitted on account of involuntary incoördinate movements of arms, legs and face but without a heart lesion. The case had been initially diagnosed by the house officer as one of chorea, but the movements became more and more

marked and the boy rapidly became blind. This occurred before any pupillary or optic disc changes were found and must have been due to the encephalitis affecting the occipital region. Later bilateral optic atrophy developed with white discs (confirmed by Mr. J. S. Bookless). The child then became silly in his attitude and gradually comatose until finally he was deeply comatose, with incontinence of urine and fæces. His respiration rate rose to practically the same value as the rate of the heart, so that it appeared as if his diaphragm was moving in response to the stimulus of each heart-beat, a condition resembling the mechanical stimulation of muscles and nerves seen in tetany. At this time there was also marked wasting of the body generally and he had to be tube-fed. It appeared as if death was imminent. The cerebrospinal fluid gave the values shown (Table XIV), and in view of these findings parathormone injections were given. After ten days the child began to improve, and rapidly became normal in the reverse order of the clinical history detailed. Most interesting of all, his optic discs regained their normal colour, except for a small patch which has become grey in the middle of the left disc. The eyesight has become normal as Mr. Bookless has testified, and recently the child has gained a scholarship. Four months after the first examination, a second showed almost normal cerebrospinal fluid values.

It appears probable that the changes seen here would have proved fatal but for the treatment. Presumably the optic discs mirrored the changes occurring in the brain and particularly in the occipital cortex; these must have been degenerative, and it must be very rare to see so complete a recovery from an optic degeneration as in this case.

Summarizing the main points of this paper, it will be seen that success in treatment of the various conditions has only resulted when the cerebrospinal fluid has shown a low calcium value, or a high phosphate value, or both, and the effects of parathormone and other forms of calcium therapy have been to correct these.

We realize that the subjects dealt with have been discussed from rather an unusual angle and that there are many possible criticisms. Perhaps the changes in the calcium and phosphate values may prove to be end-results, rather than predisposing factors—as we believe them to be. In any case, in following up this work, it will be necessary to undertake other analyses—such as the calcium and phosphate balance in these conditions—studies on which, so far, we have not touched.

We hope, however, that we shall have help and criticism to guide us in our future work, and it is for this reason that we have brought the subject to notice in what may appear to be a somewhat premature stage.

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Dr. F. PARKES WEBER suggested that it might be worth while making observations and therapeutic trials on similar lines in a rather rare class of cases, namely, in children with recurrent angiospastic attacks affecting the extremities, of the nature of Raynaud's disease. Such attacks might be termed "vasomotor tetany" from the symptomatic clinical point of view.

The PRESIDENT, Dr. LANGDON BROWN, Dr. DOROTHY C. HARE and Dr. N. GRAY HILL also spoke in the discussion.

Dr. E. C. WARNER, in reply, said that he particularly wished to stress that in carrying out these analyses very great care had to be used, as the quantities were so small. Each calcium analysis was the result of at least three estimations, and unless these came within $\pm$ 0·1 mgm. per cent., another batch was done. The same care was also taken with the estimations of the phosphate values, which were always carried out in duplicate.

Section for the Study of Disease in Children.

President—Sir HENRY GAUVAIN, M.D.

[*April* 1, 1932.]

Abdominal Sympathectomy for Hirschsprung's Disease.[1]

By L. E. BARRINGTON-WARD, F.R.C.S.

I AM taking it for granted that the features of Hirschsprung's disease are well-known to the Members of this Section.

Abdominal sympathectomy for this disease has an almost fortuitous origin. In 1924 Royle and Hunter devised an operation for relieving the spasticity of the lower extremities, by resection of the abdominal sympathetic ganglia. The merits and results of this particular operation need not be discussed here, but it was noted that one of the effects of the operation was the relief of constipation. Wade and Royle therefore applied this method to the treatment of Hirschsprung's disease, with considerable success.

In 1930 Wade reported thirteen cases, and since then cases have been reported by Judd and Adson, Rankin and Learmonth, Mercer, Clarke and Miller.

Theory has followed on practice. One of the favourite hypotheses of the origin of Hirschsprung's disease was a neuromuscular cause, although until this operation was devised the exact nature of the fault could not be determined.

In 1895 Langley and Anderson showed that stimulation of the lumbar sympathetic ganglia caused inhibition of peristalsis, with dilatation of the colon and contraction of the internal sphincter. In the ætiology of Hirschsprung's disease, as a result of Royle's work, it is now generally believed that the megacolon is due to the overaction of the sympathetic innervation of the colon and rectum. As the result of an active reflex, the colon is inhibited and the sphincters show increased tone. Removal of the sympathetic nerve supply "releases" (Trumble) the muscles of the colon and rectum.

If it is agreed that sympathectomy is a reasonable operation for Hirschsprung's disease, it becomes necessary to decide at what part in the sympathetic system can the sympathetic impulses be most efficiently interrupted. Wade and Royle divided the white ramus of the first lumbar nerve on the left side, all the mesial branches of the lumbar chain, and also the trunk itself below the fourth ganglion. Judd and Adson went further: they excised the second, third and fourth lumbar ganglia with the main sympathetic trunk, repeating the operation on the left side if the cæcum and ascending colon were affected. Rankin and Learmonth originated another operation, which seems to me a more direct attack on the problem, and which I have followed in my cases. They divided the presacral and the inferior mesenteric nerves. The colon, with the rectum, is developmentally a midline organ, and receives nerves from both sympathetic chains. It is easy to see in dissection-specimens that the inferior mesenteric ganglion receives fibres from both sides. Removal of one sympathetic trunk may not be sufficient, as happened in one of Wade's cases. Even

[1] Illustrated by cinematograph.

in removing the presacral nerves, very free decussation is found, and branches connecting with the fourth and third right lumbar ganglion, as well as the left, have to be divided. Very free removal of the presacral nerves seems to have no ill-effects. In none of the cases reported, and in none of my cases, was any effect produced on the bladder. I therefore removed these nerves thoroughly. Some connections are very small and likely to be missed, and so I find it easier, after removing the larger trunks, to dissect away the areolar tissue in a broad sheet from the level of the promontory of the sacrum, across the left common iliac vein, both common iliac arteries, and the aorta, up to the origin of the inferior mesenteric artery. This ensures removal of several small ganglia that might otherwise be overlooked. The iliac arteries and the aorta look very bare at the conclusion of the operation.

The results of the operation have been extremely good. Whereas purgatives and enemata had been necessary before operation, each of my cases within two months of the operation has reached the happy condition of a daily unaided action. The distension is less. The patients have naturally greatly improved in their general condition.

Report of Cases.—(1) T. P., male, aged 7 years, was transferred to me by Dr. Robert Hutchison. He had suffered from chronic constipation since birth. The bowels opened once or twice a week. He always defæcated standing up. He had occasional attacks of diarrhœa, and had recently required a daily enema.

On examination he was found to be a well-developed boy of fair nutrition. The abdomen was distended, especially above the umbilicus. Irregular firm masses of fæces were palpable in the ascending, transverse and descending colons. On rectal examination no stricture was found. The rectum was distended with soft fæces. Radiologically the diagnosis of Hirschsprung's disease was confirmed.

On November 17, 1931, I operated, intending to perform a colectomy, an operation which has stood me well in the past. After the exposure of the hugely dilated and distended descending pelvic colon and rectum, severe ether convulsions began and caused considerable anxiety. They could not be controlled and so the operation was abandoned and the abdomen closed. Recovery was complicated by an attack of pneumonia. On January 12, 1932, the bowel condition having become more troublesome, I decided to operate again, with the aid of rectal paraldehyde, and on this occasion determined on a sympathectomy. The anæsthetic was well taken. The abdomen was opened through a left paramedian incision, the colon was packed to the left and the small intestine to the right. A vertical peritoneal incision was made from the origin of the inferior mesenteric artery to the promontory of the sacrum in mid-line. The peritoneum was dissected laterally. A sympathetic cord, found at the level of the promontory of the sacrum, was divided and the proximal end dissected upwards to its origin from a ganglion, under cover of the left common iliac vein: it was resected. On deeper dissection, a large ganglion was found between the two common iliac arteries, and from it a large trunk was traced up to the origin of the inferior mesenteric artery, where it again broadened into a ganglion; it had several lateral connections. These were divided and all this tissue was removed. Several smaller trunks found lying along the anterior surface of the aorta, with some lateral tributaries, were removed. The aorta, from the origin of the inferior mesenteric artery to its bifurcation, and also the portion of sacrum between the promontory and the common iliac vessels, were well cleaned. Some chyle escaped from a few lymphatics along the aorta. The posterior peritoneal incision was closed with continuous catgut. The abdominal wall was closed in layers without drainage.

The patient's recovery was uninterrupted. The bowels opened naturally the first and second day after operation. On the fourth day an enema was given, and on the sixth day senna had to be administered. No aperients or enemata were required again. He was sent to the Infection Hospital on account of measles

on January 25, 1932, and readmitted February 11, 1932. When last seen, fourteen days ago, his bowels were moving normally without help. The abdomen was less distended and his general condition was excellent.

(2) A. H., male, aged 9 years. He had been constipated from birth. His abdomen had been enlarged since the age of 3 years, and he had been admitted to a cottage hospital several times for enema treatment. For the last eight months he had been

A. H.—December 1931, before operation.

March 1932, after operation.

treated at the Hospital for Sick Children, Great Ormond Street, in the medical out-patient department. The bowels only opened with enemata every second day. On examination he was found to be fairly well-developed, with a protuberant abdomen. Enlarged coils of intestine could be seen and felt. On rectal examination, no stricture was found. A barium meal showed the typical appearance of Hirschsprung's disease.

Operation, December 23, 1931.—A large colon was found, distension being most marked from the splenic flexure to the rectum. The usual operation was performed. The presacral nerves were dissected up and removed. The inferior mesenteric nerve and ganglion were also removed. The post-operative course was rather stormy. For two days following the operation, the abdomen was greatly distended, and the boy's general condition was poor. The bowels opened irregularly, and for the first fortnight enemata had to be given every other day. On return from a convalescent home, two months after operation, it was noted that "his bowels have opened regularly twice a day without enemas or aperients for the last three weeks."

(3) R. H., male, aged 10½ years. He had suffered from chronic constipation since the age of five months. The abdomen had become enlarged and he had had occasional attacks of abdominal pain.

In December, 1928, I performed a partial colectomy, removing the pelvic and part of the descending colon. The operation was successful up to a point, but the child still required a daily aperient, and occasionally had to be admitted to hospital on account of abdominal pains, which were cleared by rectal washouts. The abdomen was a little full, but no peristalsis or dilated coils of intestine were visible. I believed from my experience of the previous cases that sympathectomy would benefit him greatly. Operation was performed, February 9, 1932. There were some omental adhesions to the abdominal wall. The line of the old direct anastomosis was very good—there was no stenosis or increased dilatation above the line of suture. The left colon was still rather dilated and hypertrophied. The posterior parietal peritoneum was incised as usual and the presacral nerves and two inferior mesenteric nerves and the inferior mesenteric ganglion were resected. Recovery was uncomplicated. Syrup of senna was given on the fourth day, and since then the bowels have opened daily without assistance, except an occasional dose of paraffin, given chiefly as a precaution.

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ROYLE, *Med. Journ. Australia*, 1924, i, 77. WADE and ROYLE, *Med. Journ. Australia*, 1927, i, 137. WADE, *Lancet*, 1930, i, 136. JUDD and ANSON, *Ann. Surg.*, 1928, xxviii, 479. RANKIN and LEARMONTH, *Ann. Surg.*, 1930, xcii, 710. MERCER, *Edin. Med. Journ.*, 1931, 105. TRUMBLE, *Med. Journ. Australia*, 1931, ii, 405. CLARKE and MILLER, *Arch. Ped.*, 1931, xlviii, 9.

Discussion.—Dr. C. WORSTER-DROUGHT said that in those cases which he had seen, the immediate results of the operation described by Mr. Barrington-Ward appeared very good: it remained to see how long the effects lasted. The most important point was to decide the type of case suitable for operation. Many cases appeared to do very well and remained comparatively free from symptoms on daily doses of liquid paraffin. He had in mind two cases: the first patient, a child now aged 16, whom he (the speaker) had had under observation for the past eight years, originally came into hospital with an attack of abdominal pain and distension, but had continued free from symptoms on paraffin with a daily evacuation of the bowels. The second case was that of a man who had now reached the age of 65 in spite of megacolon; he had taken a daily dose of paraffin ever since its introduction, and had remained similarly free from any seriously disturbing abdominal symptoms.

Mr. BARRINGTON-WARD: In reply to the enquiry as to the type of case in which this operation is suitable, I cannot claim yet to speak with any assurance. These cases are too recent to allow of my being dogmatic, but the results in the short time that have elapsed are most encouraging. I know of no other procedure which could have caused so great an improvement in so short a time.

From the reported cases, there is every reason to believe that this improvement may be maintained. In estimating failures, one must remember that not every case called Hirschsprung's is a genuine example of this disease, and it is also possible that in very advanced cases, with hugely distended colons, mechanical changes may counteract any release effected by interruption of the sympathetic. Possibly colectomy may be required as well in the worst cases.

My patients have received barium enemata since the operation, and the skiagrams show a slight improvement. In common with other observers, I find that the first and most

striking effect of the operation is the regular daily action without assistance. Abdominal distension is already becoming less, but it must take many months or years for these huge colons to revert to anything approaching normal size.

Hirschsprung's Disease, treated by Excision of the Inferior Mesenteric Ganglion.—JOHN H. GIBBENS, M.B.

Stella S., the second child of healthy parents, born at full term, weighing 7 lb. 5 oz. Normal labour. Abdominal enlargement present since birth, and progressively increasing; the mother had noticed intestinal peristalsis when the child was three weeks old; there was obstinate constipation, progressively more severe since birth. Never any vomiting or abdominal pain.

First admission (September 19, 1929).—Aged 3½ years. There was enormous regular abdominal distension, the abdominal circumference being 26 in. Weight 25 lb. 4 oz. Little abnormal palpable in the abdomen because of distension and tympanites. No ascites. Very marked peristaltic waves seen, starting at the right costal margin and working diagonally across to the left groin. Motions loose, watery and offensive, during the previous seven weeks. Slight respiratory distress: costal angle very wide, almost a straight line, but air entry at both bases fairly good. General condition poor: wasted limbs and poor tone and turgor of the skin. After treatment with careful dieting, enemata and charcoal gr. 15 twice a day, the diarrhœa quickly disappeared and the child was discharged.

Charcoal in cocoa was given for two months but the child's weight dropped to 24 lb., although there were now two motions daily, of fairly normal consistency. Abdominal distension and peristalsis unchanged.

Second admission (February 17, 1930).—X-ray examination showed the typical findings of Hirschsprung's disease. On February 21 the child was sigmoidoscoped: the instrument passed easily into the pelvic colon, there being a sudden dilatation at about the region of the pelvi-rectal sphincter; not the slightest evidence of stenosis. The mucous membrane of the pelvic colon was very vascular and bled easily. A few days later the effects of physostigmine were tried, favourable results having been obtained with this drug in Germany [1]. For seven days 0·25 mgm. was given three times a day: for two days more 0·25 mgm. four times daily and for a further five days 0·5 mgm. three times a day. With this dosage not the slightest effect was noted on the degree and rate of peristalsis, abdominal distension or constipation. After a rest of one week experiments were made with acetylcholine; the dose was 0·025 grm. the first day, 0·05 grm. daily for two days, then 0·1 grm. daily for two weeks. No obvious clinical change was noted: the blood-pressure and pulse-rate remained unchanged. Discharged March 23, 1930, and given, as an out-patient, istizin, the principle of the anthracene group of purgatives, recommended by Gaedertz [2]. On the whole this tended to prevent constipation fairly effectively over six months.

Third admission (January 12, 1931).—Treated with further injections of acetylcholine for two weeks, also with high colonic washouts and given a diet with a small residue. None of these had apparently the slightest effect on the disease, so finally operation was advised.

May 6, 1931. Operation by Sir Percy Sargent.—The upper part of the pelvic colon was about the size of a football; the cæcum, ascending colon, rectum and lower part of the pelvic colon were normal. The inferior mesenteric ganglion was excised. Recovery was uneventful.

Present condition (March 20, 1932), nine months after operation. Abdominal distension much greater than previously and peristalsis still very marked. Bowels fairly regular without purgatives. Circumference of abdomen, 31 inches.

References.—[1] HOEFER and WITTGENSTEIN, *Berlin. klin. Wochenschr.*, 1921, 58, ii, p. 771. [2] GAEDERTZ, *Med. Klin.*, 1925, xxi, 1582.

Primary Hypertension in a Child.—ALAN MONCRIEFF, M.D.

Ronald P., aged 11 years, first attended the Hospital for Sick Children, Great Ormond Street, in June, 1931, on account of pains in knees and slight evening rises in temperature following influenza and tonsillitis in the preceding March. Frontal headaches were mentioned at second visit to hospital: by August, 1931, this symptom predominated. Systolic blood-pressure was then 145. Severe pains over eyes continued to occur about once a week, and occasional pains in limbs persisted. The tonsils, which were large and unhealthy, were removed in November, 1931; and following their removal the headaches became slightly less intense. The blood-pressure remained high, however, for a child of this age and is at present 140/100. Heart not enlarged (confirmed by X-ray examination); heart sounds normal, except for a variable, faint systolic murmur at apex. No evidence of renal disease. Urine completely normal; urea concentration normal (up to 4·8 per cent. at end of one hour); blood-urea normal (25 mgm. per 100 c.c.). Ophthalmic examination: No definite refractive error; retinal vessels show no obvious change. Blood-vessels of limbs not unduly easily palpable.

Family history.—Five other children in the family; none of these complains of headaches. The mother's blood-pressure is normal; other members of the family have not been examined.

Comment.—This case appears to be one of primary or "essential" hypertension, in the sense that no obvious cause can be found to account for the raised blood-pressure. A somewhat similar case with a fatal termination has been recorded by R. Hutchison and A. Moncrieff (*Brit. Journ. Child. Dis.*, 1930, xxvii, 201). In that case a girl, aged 8 years, was admitted to hospital with cerebral symptoms and a systolic blood-pressure of 180 mm. of mercury. At autopsy no cause could be found to account for this and the kidneys were normal. A brief reference to the scanty literature on this subject will be found in that paper.

Juvenile Neurosyphilis, with Pupillary Changes as the sole Clinical Manifestation.—C. WORSTER-DROUGHT, M.D.

R. K., male, at the age of 9 years was brought to hospital on account of inequality of pupils.

History.—Four years ago he bumped his head (right frontal region) on a lamp-post. Shortly after this his parents noticed that his pupils were abnormal. He attended an ophthalmic clinic where it was noted that the pupils were unequal and that the left pupil failed to react. The case apparently was regarded as one of "traumatic Argyll Robertson pupil." A few weeks ago the patient was seen by Mr. L. Savin, who was dissatisfied with this opinion and referred him for neurological examination.

Physical examination.—Healthy-looking child, well nourished; some depression of nasal bridge and tendency to frontal bossing. Height, 4 ft. 2 in.; weight, 3 st. 12 lb.

Pupils: Left dilated and larger than right; left pupil inactive to light and accommodation; right pupil sluggish both to light and accommodation; eyes hypermetropic. Fundi normal. Other cranial nerves normal. Arm-, knee- and ankle-jerks brisk and equal; abdominal reflexes brisk and equal; plantars flexor; coördination normal.

The only sensory abnormality present is that vibration sense is somewhat diminished over the bony surfaces of the legs.

Teeth: Incisors slightly peg-shaped. Heart and lungs normal. Blood-pressure 120/70. Blood Wassermann reaction positive. Cerebrospinal fluid: 9 lympho-

cytes per c.mm.; total protein 0·04 per cent.; globulin positive; Wassermann reaction positive; Lange: 3433310000.

Commentary.—The few physical signs that are present in this case suggest that the neurosyphilis approximates more to the tabetic type than to that of juvenile dementia paralytica. Tabes dorsalis is a rare condition in childhood, but this is the fourth case I have shown before this Section during the past eight years [1]; in the other three, the signs of spinal cord involvement were much more definite. Dr. Wyllie has also shown one case in a child aged 13 years [2]. In other Sections, one case in a child aged 11 years was shown by Dr. Harris [3] and four older cases (patients between the ages of 20 and 26 years) have been demonstrated by different physicians [4].

The father and mother of this patient are both alive and well and neither shows any signs of neurosyphilis or of syphilis. The mother has had no miscarriages or stillbirths, but her blood yields a strongly positive Wassermann reaction. The father gives a negative Wassermann reaction. There are four children in the family, of whom the patient shown is the eldest. The others—girl aged 8 years, boy aged 2 years, boy aged 5 months—are well and present no abnormal physical signs.

The present case is well below the average age incidence of recorded cases (15 years); the youngest case—in which the onset occurred at 3 years of age—appears to have been described by Mingazzini and Salvadori. A point of interest in the case is the absence of any physical signs in the parents beyond the presence of a positive blood Wassermann reaction in the mother.

The prognosis in juvenile tabes appears to be relatively good. A case which I showed before the Section in 1924, that of a girl aged 10 years, with double Argyll Robertson pupils and absent knee- and ankle-jerks, as well as positive Wassermann reactions in blood and cerebro-spinal fluid—is still doing well at the age of 18.

REFERENCES.

[1] *Proceedings*, 1924, xvii (Sect. Dis. in Child. 18 and 19). [2] WYLLIE, W. G., *ib.*, 1926, xx, 325 (Sect. Dis. in Child. 15). [3] HARRIS, W., *ib.*, 1926, xx, 385 (Sect. Neur. 13). [4] RIDDOCH, G., *ib.*, 1924, xvii (Sect. Neur. 37). RANDLE, A., and MAPOTHER, E., *ib.*, 1927, xx, 629 (Sect. Psych. 1). WORSTER-DROUGHT, C., and ALLEN, I. M., *ib.*, 1929, xxii, 607 (Clin. Sect. 45). VINER, G., *ib.*, 1928, xxii, 443 (Sect. Ophth. 21).

Aphonia and Congenital Heart Disease.—REGINALD LIGHTWOOD, M.D. (By permission of F. G. POYNTON, M.D.)

D. B., female, aged 4½ months, believed to be the subject of congenital heart disease, was able to cry normally for the first five weeks. Since then she has not been able to make a noise when she attempts to cry. The onset of this aphonia was sudden. She is cyanosed only after prolonged attempted crying.

Examination: Cry very weak; respiration "pumping" in type, with indrawing of epigastrium and of lower costal margin, as seen in infants with congenital heart disease. Larynx moves on swallowing and shows some degree of excursion with respiration.

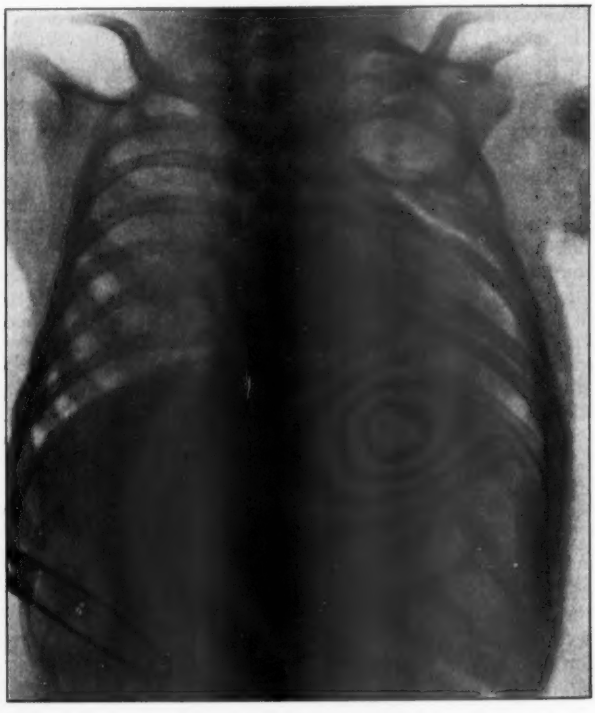
Lungs normal. Heart enlarged; a systolic murmur at apex. Skiagram of thorax confirms the presence of cardiac enlargement and shows a cardiac shadow of unusual shape.

The interest of this case lies in the question of the relationship between the aphonia and the congenital heart lesion. Left recurrent laryngeal nerve involvement has been described in cases of patent ductus arteriosus and a dilated left auricle also might exert pressure on this nerve. In the present case, however, on laryngoscopic examination, the vocal cords can be seen to abduct freely, though their adduction seems imperfect, and such findings are not characteristic of organic recurrent laryngeal nerve involvement.

Intra-uterine Fractures.—A. S. HALL, M.B. (introduced by Dr. JAMES MAXWELL).

V. P., female, aged 10 weeks.

The child was born naturally at full term. No abnormality was noticed at birth. Since then she has had a cough.



Intra-uterine fracture of ribs.

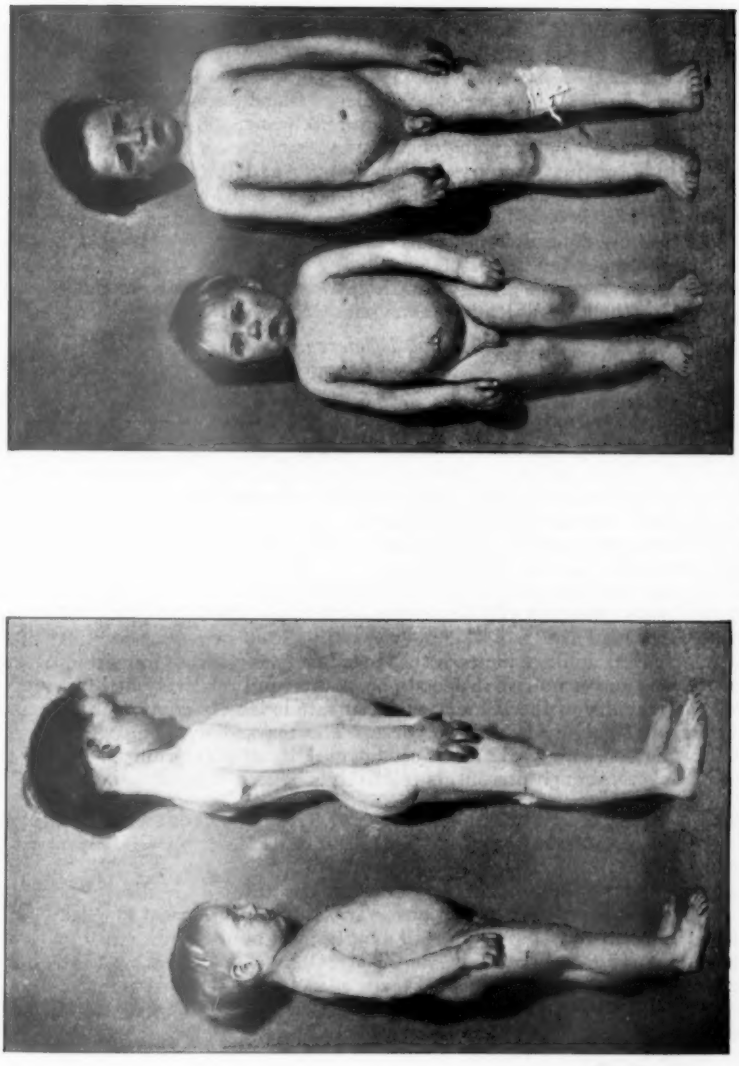
On examination, at the Royal Chest Hospital, she was found to have retraction of the left chest with impairment of note and poor breath sounds, particularly over the left upper lobe.

The skiagram shows deformity of the fourth to the eighth ribs on the left side.

The mother states that when seven months pregnant she fell on her abdomen.

Renal Dwarfism.—R. W. B. ELLIS, M.D. (by permission of A. G. MAITLAND-JONES, M.D.).

A. N., male, aged 4 years. Mother, father and one sibling alive and well. Full term, normal delivery. Birth weight 8½ lb. Breast-fed fourteen months. Walked at sixteen months. First tooth at age of nine months. Patient appeared normal until age of two years, when he began to drink an excessive amount of fluid and to pass very large quantities of urine. Polydipsia and polyuria have continued since this time and he suffers extreme distress if fluids are withheld. He has not increased



A. N. with normal control of four years, showing degree of dwarfing with absence of deformities.

in height or weight during this period, but apart from occasional vomiting has been in good general health.

On examination.—An active, normally intelligent child of four, weighing 24 lb. 14 oz. (normal for age, 35 lb.). Height 32 in. (normal, 38 in.). Circumference of head 19 in. Chest 19¼ in. Abdomen 20½ in. Apart from a prominent abdomen, he is sturdy and well-proportioned. Liver and spleen not felt. No rachitic deformities of limbs. Teeth well calcified. Skin shows slight yellowish tinting with uniformly "muddy" staining of sclerotics. Blood-pressure 105/76.

Radiological report.—Hands: Delay in appearance of centre for cuneiform. Wrists: Splaying and some cupping of metaphyses of radius and ulna. Fibula and tibia: Flattening of juxta-epiphyseal lines upper and lower extremities of both bones. There is no widening of actual epiphyses seen at any point. Pituitary fossa is possibly a little deep but probably within normal limits.

Cystogram showed no deformity of bladder; no reflux into ureters. Average daily fluid intake approximately 1,600 c.c.

Urine, neutral. Specific gravity, 1,007. Albumin, very heavy cloud; no sugar; few red cells; epithelial cells; amorphous phosphates.

Renal Efficiency.

	Phenolsulphonephthalein	Urea concentration
1st vol. 132 c.c.	2·2%	—
2nd vol. 70 c.c.	2·6%	0·63%
3rd vol. 90 c.c.	3·3%	0·66%

Blood-urea, 0·073%; serum calcium, 8·5 mgm. per 100 c.c.; plasma phosphorus, 4·3 mgm.; plasma phosphatase, 19·3 units per 100 c.c.

Blood: Total proteins, 7·0%; albumin, 4%; plasma chlorides, 0·66 grm. % as sodium chloride. Van den Bergh: Negative direct reaction; indirect = 0·1 mgm. bilirubin % (normal); fragility of red cells, normal. Wassermann reaction, negative. Mantoux, negative.

Blood-count.—R.B.C. 5,700,000; Hb. 84%; C.I. 0·73; W.B.C. 24,000. *Differential*: poly. neutros. 51%; eosinos. 9·5%; small lymphos. 24%; large lymphos. 10%; large hyals. 5·5%.

The biochemical findings indicate that in spite of very severe impairment of renal function there is as yet no rise in blood phosphorus and relatively little rise in blood urea, i.e., the inability of the kidney to concentrate is largely compensated for by the extreme degree of polydipsia and polyuria. The marked dwarfing which has been evident for the past two years is unaccompanied by any deformity, and the X-ray evidence of rickets, though present, is relatively slight.

Three Cases of Familial Congenital Cystic Disease of Kidney and Liver.—By REGINALD LIGHTWOOD, M.D., and G. H. LOOTS, M.D. (by permission of HUGH THURSFIELD, M.D.).

Synopsis.—Four children in this family are known to have disease of the liver, and three of them have been under observation at the Hospital for Sick Children. Peter, third in family, died aged 1 year 10 months from fibrosis of the liver, with cystic changes and congenital cystic kidneys. The details of his disease and the autopsy are reported in Case I. Peggy (Case II) now aged 4 years, shows evidence of hepatic disease and has slight albuminuria. John (Case III), now aged 1 year 11 months, has hepatic disease, enlarged kidneys and albuminuria.

Case I.—Peter, aged 1 year 10 months at death.

Past history: At 1 year of age ceased to gain weight; difficulty in feeding; abdomen became enlarged.

Examination: Moderately anæmic, no fever. Abdomen: Enlarged, veins dilated. Liver: Enlarged, especially the left lobe; hard, not tender, with a sharp edge three finger-breadths below costal margin. Spleen enlarged to level of umbilicus. No other masses in abdomen and no ascites. Wassermann negative. Blood-count:

R.B.C. 4,500,000 per c.mm.; hæmoglobin 45%; W.B.C. 12,000 per c.mm. Urine contained blood and pus. While in hospital there were bouts of swinging temperature up to 105° F., which were judged to be due to the urinary infection. Van den Bergh: Direct reaction negative, biphasic reaction negative, indirect test = 0·5 units of bilirubin. Fragility of red cells slightly increased (trace of hæmolysis in 0·57% of sodium chloride). Blood-urea, 49 mgm. per 100 c.c. Urea-concentration test showed some impairment of function:—

	Urea	Urine c.c.
1st hour	1·16	20 c.c.
2nd „	1·20	1 c.c.
3rd „	1·00	1 c.c.
4th „	2·12	2 c.c.

Purpura was seen from time to time.

Autopsy (Dr. W. G. Wyllie).—Abdomen: No ascites. Liver: Considerably enlarged, reddish brown, surface finely granular, firm. On section: Macroscopically, marked diffuse fibrosis; microscopically, congenital hepatic fibrosis with greatly dilated bile channels, giving the section a cystic appearance.

Spleen: About five times normal size, firm, smooth surface. On macroscopical section—dark, red and homogeneous.

Kidneys: Both about two and a half times normal size, showing evidences of fœtal lobulation. Capsule stripped with difficulty, leaving a finely granular surface. On macroscopic section the pyramids appeared white and fibrotic and felt very hard. The cortex was swollen, was streaked with fibrous tissue and showed numerous very small cysts; in places it had softened and had a greenish tint and almost gelatinous appearance. The calyces were dilated.

Thorax: No abnormality. Lymphatic glands not enlarged.

Case II.—Peggy, aged 4 years, well-nourished, pale; bruises on leg. Skeleton: Square rachitic head, slight Harrison's sulcus; bones and epiphyses normal. Heart: Not enlarged, systolic murmur heard over præcordium. Lungs: Normal. Lymphatic glands: Not enlarged. Abdomen: Spleen enlarged two finger-breadths below costal margin; firm, smooth and mobile. Liver enlarged two finger-breadths below costal margin; firm, surface irregular, not tender. No ascites. Kidneys not felt. Urine: A trace of albumin present on admission.

Case III.—John, aged 1 year 11 months, pale and flabby; hare lip; cirrhotic facies. Skeleton: Rachitic square head, anterior fontanelle just closed, bones and epiphyses normal. Heart not enlarged; ? systolic murmur at apex. Lungs normal. Lymphatic glands not enlarged. Abdomen enlarged; dilated veins: umbilical hernia; ascites. Spleen enlarged one finger-breadth below costal margin. Liver: Enlargement chiefly of the left lobe, a sharp firm edge being felt in the epigastrium. Kidneys both enlarged, irregular in shape. Urine: Albumin present and some red blood-corpuscles.

Discussion.—Dr. LIGHTWOOD said that he was in a position to add further details regarding the family history of these cases. The disease had occurred in four members of one generation and no evidence of other relatives being similarly affected had so far come to light. The condition was associated with hare lip deformity in this family.

Still[1] had reasoned that the cysts in the liver were not merely dilated bile ducts, for jaundice never occurred, but true cysts of developmental origin. The hepatic fibrosis was also congenital and developmental, and in no sense a "cirrhosis" of inflammatory origin. It had already been pointed out that the disease might be hereditary and occur in several members of the same generation[2].

Dr. PARKES WEBER said that microscopical examination of the liver from cases of congenital polycystic kidneys often showed great excess of interlobular fibrous tissue in addition to cysts. The change (as the familial character in some instances helped to confirm) was of congenital-developmental nature and not due to any cirrhosis or fibrosis from disease

1 G. F. STILL, *Trans. Path. Soc.* (Lond.), 1898, xlix, 155.

2 KANTHACK and ROLLESTON, *Virchow's Arch.*, 1892, cxxx, 488. BUNTING, *Journ. Exper. Med.*, N.Y., 1906, viii, 271.

in the ordinary sense. Dr. Weber maintained therefore that in these cases it was preferable and strictly correct to speak of "cystic dysplasia of the kidneys" and "cystic dysplasia of the liver."

Lipodystrophia Progressiva.—BASIL LONGBOTHAM, L.R.C.P., M.R.C.S. (for A. G. MAITLAND-JONES, M.D.).

F. E., a boy, aged 11 years. One of eight children; others alive and well. No Hebrew blood.

Seen in January, 1931, complaining of wasting of arms and face for last six months; onset noticed shortly after a dog-bite. General health good.

Lipodystrophia progressiva.

On examination.—Face, upper limbs and upper part of chest very wasted owing to absence of subcutaneous fat. The muscles appear to be intact. Abdomen normal. No excess of fat on legs and buttocks. Skin rather dry and hair coarse. No tremor of hands; no depression. Penis normal; testicles infantile.

Skiagram of chest clear. Mantoux test negative. Blood calcium = 10·5 mgm. per cent.

Dr. PARKES WEBER said that in some cases of "lipodystrophia progressiva" progress was not maintained, and the lipodystrophia might remain limited to the face, or the face and neck. The present patient was an example of the extremely rare almost fully developed cases in males. Very few such cases had been recorded.

Fusion of Middle-third of the First and Second Ribs.—DAVID LEVI, M.S., F.R.C.S.

Boy aged 8 years seen by school doctor and sent to hospital on account of a lump at the inner end of the first right rib. There is a history of an injury four years ago. The boy is perfectly well and is apyrexial.

The skiagram (see figure) shows fusion of the first and second ribs in the middle-third of their course on the right-hand side. The condition appears to be congenital.

Right. Left.

Fusion of middle-third of first and second ribs, right side.

Fusion of the sternal ends of ribs occurs in old age and is due to ossification spreading into and from the costal cartilages. Fusion of the vertebral ends of ribs occurs following lesions of the intra-thoracic contents, especially in long-standing collapse of the lung.

Fusion of the middle-third of the first and second ribs is a rare condition. There is no instance recorded in anatomical textbooks.

Pseudo-hermaphroditism.—DAVID LEVI, M.S., F.R.C.S.

Child registered at birth as a girl. Mother brought child to the Infants Hospital to ascertain its sex.

On examination.—Well-developed infant, aged 18 months. Penis stunted. Hypospadias of urethra. Cleft scrotum. There is a well-marked development of the pubic hair.

Examination of the abdomen is negative. There are no palpable suprarenal tumours. The patient appears to be suffering from an advanced degree of hypospadias, but will be kept under observation. If the lesion is a simple hypospadias the child is probably a male. There may, however, be a complicating pituitary adrenal tumour which at the present time is so small as to escape discovery. If this be the case the child may prove to be a female.

Section of Obstetrics and Gynæcology.

President—Mr. VICTOR BONNEY, M.S.

[*March* 18, 1932.]

An Evaluation of the Incidence of and the Maternal Disability following Eclampsia and Albuminuria.

By JAMES YOUNG, D.S.O., M.D., F.R.C.S.E., F.C.O.G., JESSIE C. B. SYM, M.D., D.P.H., and ELSIE V. CROWE, M.B., F.R.C.S.E.

The extent of the problem.—We have no data by which to compute accurately the incidence of or the damage inflicted by the toxæmias of the later months of pregnancy (pre-eclampsia and eclampsia, albuminuria, hypertension) in the community at large. From the Registrar-General's figures we obtain the measure of the deaths occurring during pregnancy, labour and the puerperium, but we do not know the incidence rate during pregnancy, and there are no data by which we can judge either the extent of the disability sustained by those who survive the puerperal period or the deaths occurring later as a consequence of this damage, which naturally do not appear in the official statistics of maternal mortality.

In 7,790 successive and unselected cases attending the antenatal department of the Edinburgh Royal Maternity and Simpson Memorial Hospital, there were 477 cases treated as pre-eclampsia, albuminuria or hypertension without albuminuria. This gives a rate of 6% for the class of patient attending this clinic. It should be specially noted that this figure applies to the routine and unselected attendances and excludes women specially referred to the hospital for diagnosis or treatment. Of the total of 477 cases diagnosed as toxæmia at the clinic, 209 (or 44%) were admitted for treatment. This means that of the 7,790 patients reporting for routine antenatal care, 2·7% were admitted for treatment because of late pregnancy toxæmia.

We have said that we have no accurate data of the toxæmic rate for the community at large from which we can estimate the extent of the problem on national lines. It is true that the textbooks give figures, but we may conclude that these, for the most part, are merely tentative and undocumented. Thus, Eden and Holland state that in this country the rate is somewhere between 3% and 5%. Other observers give much higher rates. On the other hand, in the antenatal department of the East End Maternity Hospital in London the rate is only 2%. It is commonly stated that Scotland shows a higher rate than England and Wales, and the official

death statistics of the two countries tend to confirm the view that toxæmia is relatively more lethal, and therefore, presumably more common, in Scotland than in England and Wales. Thus, in 1930 the respective death-rates for Scotland and England and Wales were 1·2 and 0·72 per 1,000 live births.

It is probably a safe assumption that the rate for England and Wales lies somewhere between that of 2% for East London and the Edinburgh figure of 6%. If, for purposes of study, we accept 4%, we get a figure probably within reasonable distance of the national rate. Calculated on the basis of the official data for 1930 we get a total of 25,952 or, in round figures, 26,000 women suffering from late pregnancy toxæmia out of a total of 648,811 live births. The total puerperal deaths for this year were 2,854, and of these, 467 were attributed to puerperal convulsions and albuminuria. Thus, utilizing our hypothetical figure of 26,000 as the total cases of toxæmia, we arrive at the conclusion that 1·8% of this total ended fatally.

It would be an advantage if we could estimate, amongst the women suffering from late pregnancy toxæmia, the total risk of this toxæmia passing over into eclampsia. We cannot, of course, arrive at this directly, as there are no accurate data to indicate the eclamptic rate during childbirth in the community at large, and the Registrar-General's statistics do not even separate out the eclamptic deaths from the total mortality attributable to toxæmia. There are, however, data now available by which we can obtain some approximation to the information we require. Thus, the Interim Report of the Maternal Mortality Committee showed that the examination of 1,596 deaths due to puerperal causes revealed a total of 218 eclampsias, that is, 13·6%. If we utilize this figure of 13·6 to obtain the eclamptic death-rate for the year, we find that out of a total of 2,854 maternal deaths during 1930, there were 388 caused by eclampsia. The London Committee, appointed by the Section of Obstetrics of the Royal Society of Medicine some years ago, found that a study of 2,005 cases of eclampsia throughout the country showed a total mortality-rate of 22·5%. Accepting this figure for the purpose of our investigation, we deduce that during 1930 in England and Wales there were 1,680 cases of eclampsia, or 1 in 386 live births. From this we reach the tentative conclusion that *6·4% of all the toxæmia cases developed eclampsia.*

It must, we think, be admitted that this is a surprising—and at the same time, a disquieting—result, having regard to the now commonly accepted view that, whilst we cannot prevent the development of toxæmia, we can by appropriate antenatal care largely obviate the supervention of the graver manifestations. Thus, Gibberd has shown that in a total of 8,000 district cases confined under the care of Guy's Hospital there were 300 cases of albuminuria (3·7%) with only two cases of eclampsia, one in a woman who had refused to have labour induced for toxæmia. In this practice, therefore, the risk of eclampsia in toxæmic women under adequate antenatal care is only 1 in 300 or 0·3%. Oxley, in the East End Maternity Hospital, London, gives a series of about 200 cases of albuminuria with only one eclampsia, or 0·5%, and no deaths. There is, thus, strong evidence that, unable though we are because of our ignorance of ultimate causes, to obviate toxæmia, we can at least by appropriate measures safeguard women against the major risks of this when it does develop. The fact that under present conditions about 6% or 7% of toxæmic cases pass over into eclampsia with its enormous risk to life must be considered as a severe reflection on our current methods of maternity.

Recurrence of toxæmia.—It may, we think, be now taken as firmly established that the pre-eclamptic and the eclamptic type of toxæmia is liable in a high degree to recurrence in succeeding pregnancies. Since our first communication [1] on this question published in 1927, when we showed a recurrence rate of 31·9% in cases of eclampsia and of 35·6% in cases of "albuminuria," further papers have appeared by Gibberd [2] and others which serve to emphasize the same facts. If we add to the risk of recurrence quâ toxæmia the risk of abortion, premature or stillbirth

without toxæmia, the obstetric history of women with this taint assumes a very serious aspect. Thus, in a second communication [3] we showed that 82 out of a total of 144 subsequent pregnancies in cases of toxæmia (eclampsia and "albuminuria") were vitiated by toxæmia or intra-uterine disaster to the fœtus without toxæmia, that is 57%. Furthermore, at least three out of the 93 women, who became pregnant subsequent to their leaving hospital, died from toxæmia in a subsequent pregnancy, that is, more than 3%.

Table I represents the result of an analysis of a further series of 84 toxæmic cases who had 120 subsequent and completed pregnancies.

TABLE I.—ANALYSIS OF 120 SUBSEQUENT AND COMPLETED PREGNANCIES IN 84 CASES OF TOXÆMIA.

Normal	42	...	35·0%	
Toxæmic	67	...	55·8%	65%
Premature labour, abortion, etc., without toxæmia	11	...	9·2%	
Total ...	120	...	100%	

Maternal disability following toxæmia.—With the object of estimating the nature and the incidence of the disability following the late pregnancy toxæmias we instituted in the year 1926 at the Edinburgh Royal Maternity and Simpson Memorial Hospital a Toxæmia Clinic for the following-up of such cases treated in the hospital. This clinic meets once weekly and on an average from ten to twelve patients report at each session. The post-natal cases attend for as long a period as is required and, in addition, those cases which become again pregnant and in which special ante-natal supervision is desirable.

It early became noticeable that a large proportion of these cases exhibit an impairment of health in which it is impossible to incriminate any one system, such as the urinary, the vascular, and so on. The disability partakes rather of the nature of a "chronic debility," inability for mental or physical exertion and a tendency to tire easily. With these more general features there may be evidence of persisting renal or cardio-vascular disease, and anæmia is common. In our classification we have adopted the following arbitrary terms; "impairment of health" means an appreciable loss of vigour and health as contrasted with the original state, and it also includes cases of persisting hypertension or albuminuria with or without evidence of ill-health; "poor health" means a graver degree of the same manifestations whilst "shattered health" means that the patient is reduced to live the life of a chronic invalid.

The tables represent the findings in the last 63 eclamptics and 176 "albuminurics" studied.

TABLE II.—SUBSEQUENT HEALTH IN 63 CASES OF ECLAMPSIA.

Good health	29	... ...		46%
Impaired health	21			
Poor heath	9			
Shattered health	3	13 = 20·6%	34 = 54%	
Died...	1			
	63			100%

TABLE III.—SUBSEQUENT HEALTH IN 176 CASES OF ALBUMINURIA.

Good health	93	... ...		52·9%
Impaired health ...	43			
Poor heath	17			
Shattered health ...	14	35 = 19·9%	78 = 44·3%	
Died	4 = 2·3%			
Ill from other causes ...	5	... ...		2·8%
	176 ...	... ...		100%

TABLE IV.—SUBSEQUENT HEALTH IN 239 CASES OF ECLAMPSIA AND ALBUMINURIA.

Good health	122		... ...		55·2%
Impaired health ...	64				
Poor health	26				
Shattered health ...	17	48 = 20%		112 =	42·7%
Died	5 = 2·1%				
Ill from other causes ...	5	...	... ...		2·1%
	239				100%

These figures show that in the cases admitted to the hospital for late pregnancy toxæmia the follow-up reveals a disability or death-rate of 42·7%, whilst there is grave involvement of health in 20%. There was evidence that in all five fatal cases death could be attributed to the damage inflicted by the toxæmia. This gives a subsequent death-rate of 2·1%.

As we should expect, the risk of disability is marked in those women who have had two or more toxic pregnancies, and in Table V is represented the study of forty such patients.

TABLE V.—SUBSEQUENT HEALTH IN 40 CASES OF RECURRENT TOXÆMIA.

Good health ...	15			37·5%
Impaired health ...	10			
Poor health ...	7			
Shattered health ...	6	15 = 37·5%	25 =	62·5%
Died	2			
	40			100%

In 15, or 37·5% the health was poor or shattered or death had occurred (5%) whilst the total disability rate has risen to 62·5%.

We may assume that this high disability-rate in the case of women who have suffered from toxæmia in successive pregnancies is a direct consequence of the greater total period during which the organism has been exposed to the assault of the poisons, as compared with those women who have had only one toxæmic attack. In Table VI we have represented the result of an analysis of the average risk in relation to the total duration of the toxæmia as obtained by adding together the weeks in the various pregnancies in which this abnormality was present. For reasons which are sufficiently obvious, it is often impossible to ascertain this information with any accuracy and this explains the disparity between the numbers of the cases under the different heads in this and former tables.

TABLE VI.—FIRST SERIES—122 CASES.

	No. of cases	Total duration of toxæmia in weeks
Good health	52	3·0
Impaired health	70	6·0

SECOND SERIES—50 CASES.

Good health	24	4·5
Impaired health	26	6·7

It thus becomes apparent that the risk of disability increases on the average with the period over which the patient is exposed to toxæmia.

It has to be noted that the figures represented in Tables II to V relate to two classes of case: (*a*) those referred to the antenatal department or admitted directly because of the existence of toxæmia. This category includes a considerable proportion of women who are gravely ill before they arrive at the hospital and who are selected in this sense; (*b*) those cases admitted from the routine antenatal department which may, therefore, be taken to represent unselected samples from the population. It is

from this class of case alone that we are enabled to draw any deductions that are capable of being applied in an effort to estimate the disability rate of the community at large. In this connection, however, we have to note that there is the chance that this latter class may include women who naturally seek the services of the institution because of some difficulty or abnormality, such as fœtal death, during their previous pregnancies, and who in this sense form a selected group. To exclude the tendency these might have to inflate our disability rate we have set out the results of the following-up of 91 patients who were admitted from the routine antenatal clinic because of toxæmia during their first pregnancy. It must, of course, be admitted that this rigid selection cannot be considered to give a fair representation of the full extent of the disability rate present in the community at large, because it excludes the large group of cases of recurrent toxæmia which, as we have seen, exhibit a very high disability rate. Further, it must tend to restrict the intensity of the toxæmia in so far as it refers only to women who have had the advantages of that rest and other treatment which is denied to many women in domiciliary practice. For such reasons we are justified in concluding that we obtain by this segregation a minimum estimate.

TABLE VII.—SUBSEQUENT HEALTH IN 91 UNSELECTED CASES ADMITTED FROM THE CLINIC BECAUSE OF TOXÆMIA IN THEIR FIRST PREGNANCY.

Good health	53	58·3%	
Impaired health ...	26	38 = 41·7%	
Poor health	12		
	91	100%	

The totals are too small to allow of anything more than a provisional conclusion. So far as they go they suggest that the minimum rate of disability following toxæmia may be placed at over 40%.

By applying this figure to the community at large we get, on the basis of 26,000 in the year suffering from pregnancy toxæmia and after deducting 500 (in round figures) for the deaths due to eclampsia and albuminuria, a minimal total of over 10,000 women in England and Wales who annually suffer more or less persisting disability from the pregnancy toxæmias. This estimate is based upon a hypothetical incidence of pregnancy toxæmia of 4%. If, on the other hand, we assume a 3% rate we still get a total annual disability rate of over 7,000.

Management of toxæmia.—These findings demonstrate that expectant treatment of a toxæmia in the interests of the child is apt to prejudice the health of the mother in a greater or less degree. They demonstrate, also, the necessity for the most rigid antenatal supervision of all toxæmic cases, so that termination of pregnancy can be carried out so soon as the circumstances warrant this being done. It is notorious that the disease is treacherous, in the sense that the general clinical condition of the patient may give no indication of the gravity of the danger, and unless constant watchfulness is possible, a patient, who to-day has few of the subjective symptoms or objective signs that in other classes of disease rouse alarm, may to-morrow be dead.

It may be laid down as an established fact that if we are to grapple with the problem (*a*) we must provide for each pregnant woman an attendant—midwife or doctor—thoroughly conversant with the significance of antenatal supervision and the meaning of the first signs of the disease; and (*b*) we must educate women to place themselves under the care of their attendant before the period of danger arrives, that is, at the latest, by the sixth month of pregnancy.

As a further point for consideration there is (*c*) the fact that, in the case of many women, removal to hospital is necessary for them to obtain the treatment which is imperatively demanded in the great bulk of the toxæmias, namely, complete rest, dieting and constant supervision. It may be laid down as an axiom in the management of such women that the supreme function of the domiciliary attendant is the

early recognition of the disease and the immediate dispatch of the patient to hospital. The fact that probably at least 10,000 to 15,000 cases each year in England and Wales require such institutional treatment raises the question of the need of an extension of our hospital services if we are to deal adequately with the problem.

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Discussion.—Professor F. J. Browne said that he had never heard Dr. Young read a less controversial paper. He was in agreement with almost everything that the speaker had said, but in his opinion he had not gone far enough. If the incidence of chronic nephritis after pre-eclampsia was to be materially diminished the diagnosis must be made earlier. For this purpose it was of no use to examine the urine occasionally in the later months of pregnancy; the tests should be carried out regularly every month until the thirtieth week—every fortnight until the thirty-sixth week and every week thereafter. It was even more important to examine the blood-pressure at the same time. In a recent paper he had pointed out that a rise of blood-pressure was generally the earliest sign of pre-eclampsia and might precede the development of albuminuria by weeks or even months. During this pre-eclamptic stage the patient might have no symptoms to draw attention to her condition and might even have no objective signs except hypertension. Such patients were, in his opinion, in a dangerous condition and should be as far as possible resting in the recumbent position. In his experience treatment by elimination or by special diet was disappointing, and only too often premature termination of the pregnancy seemed to be the only method of arresting the trouble. Many more antenatal beds were required for the treatment of these cases than were at present available.

Mr. L. Carnac Rivett said that since Dr. Young had read his original paper a few years ago, he, Mr. Rivett, had been carefully watching for cases in which there was trouble subsequent to eclampsia or albuminuria. In his experience patients who had had eclampsia in a previous pregnancy had no trouble at all in a subsequent pregnancy.

With albuminuria it was rather different, as in many of the cases there was pre-existing nephritis, and this would certainly mean increasing trouble with every pregnancy, one great feature being the appearance of albumin in the urine very early in pregnancy. In many of these cases the patients had a kidney lesion, which caused no disability or albuminuria in ordinary life, but when the additional strain was put upon the patients by pregnancy they failed under it. In assessing the damage, as shown by subsequent ill-health, Dr. Young had, it appeared, omitted to have any controls. In his, Mr. Rivett's, opinion and experience, a large number of women who had an apparently normal pregnancy and labour suffered a good deal from impaired health for many years afterwards, in fact he would say that comparatively few women enjoyed their previous robust health after they had a baby. In regard to abortion, this was even more striking. The normal abortion rate was something like 20% of the population. Therefore a 9% abortion rate was lower than the average, and he could not see that Dr. Young had succeeded in establishing that the albuminurias in particular produced abortion.

Dr. J. S. Fairbairn said that he had recognized early in his obstetric experience that late disability from renal disease after a toxæmic pregnancy was frequent and was liable to escape attention owing to the remoter period at which its effects became manifest. His impression was that the cases in which these effects were most commonly met were rather those with an onset of albuminuria more gradual and earlier in the pregnancy than in those that actually had eclampsia. There was a tendency to think of patients in all cases of albuminuria of pregnancy as prospective eclamptics, and for that reason he disliked the term "pre-eclampsia" as begging the question. During recovery from eclamptic convulsions the most striking feature was often the rapid diminution of albumin from urine which previously had boiled nearly solid, whereas in cases of albuminuria of more gradual onset but resistant to treatment, recovery after the termination of the pregnancy was usually both more gradual and less likely to be complete. Subsequent pregnancies in the latter type almost invariably showed return and aggravation of symptoms, and these were the cases that seemed to him to

be most commonly left with renal deficiency and the lowered expectation of life that went with it.

Lady BARRETT said that the statistical result obtained by investigation into the after-effects of toxæmias was important and illuminating. She wondered whether failure in health had been in any way coördinated with estimation of renal efficiency after confinement. Such investigation was important as an aid to advice with regard to the necessity of avoiding future pregnancies. The type of case with high blood-pressure was to be distinguished from the cases with but slightly raised blood-pressure and albuminuria. She had found that high blood-pressure was by no means immediately relieved by delivery, and therefore somewhat doubted the advantage of immediate induction in that group.

Dame LOUISE MCILROY said in her experience toxæmia with fits was rarely recurrent. Patients were liable to suffer from kidney damage in subsequent pregnancies Apart from the acute fulminating type of toxæmia and antepartum hæmorrhage, the death-rate was low. Preventive measures, such as careful supervision by a dentist during pregnancy, dieting, and frequent examination of the patient's general and obstetrical progress were important factors. Every expectant mother should be seen at least once by a doctor in the case of midwives' patients. Albumin in the urine was looked upon as a danger-signal, but it was not always present before the onset of acute symptoms. Examination for the presence of the colon bacillus and—if it was found—its treatment, would do much to lessen the risks of toxæmia. She had always obtained invaluable help from the biochemical investigations of the blood and urine. All cases of toxæmia required careful postnatal supervision. In her experience many cases were followed up for a number of years. Methods for the prevention of a future pregnancy should be advised until the patient was considered fit to undertake its risks.

Granulosal-Cell Tumours of the Ovary.

By E. H. LEPPER, M.B., B.S., A. H. BAKER, M.D., F.R.C.S., and D. M. VAUX, M.D.

GRANULOSAL-CELL tumours of the ovary are comparatively rare, judging by the small number of cases reported in the literature. The seven cases here described have, however, been collected from one hospital over a period of nineteen years. This suggests that their occurrence is frequent enough to give them a definite clinical importance.

The following is a brief description of the most recent case of our series :—

Case No. 7. Clinical history.—Mrs. W., aged 60, attended the Elizabeth Garrett Anderson Hospital on account of irregular floodings, from which she had suffered for four months. The menopause had occurred eight years previously. Three years ago there had been a slight vaginal hæmorrhage.

Vaginal examination revealed a bulky uterus, with a normal cervix. There was bleeding from the uterus at the time of examination. On bimanual examination a firm mass was felt in the pelvis. At operation, this firm mass proved to be an ovarian tumour, the size of a grape-fruit. The uterus contained a fibroid. Total hysterectomy was performed with bilateral salpingo-oöphorectomy.

Recovery was uneventful. Eleven months after the operation the patient was quite well.

Pathological findings.—The specimen removed at operation consists of a smooth, rounded tumour 4½ in. by 3½ in. by 3 in., partly solid, partly cystic. On section, about one-third is seen to be composed of closely packed cysts containing mucoid material, while the remaining two-thirds resemble a fibroma.

Histological examination of the cystic part shows spaces of varying size lined by a single layer of columnar epithelium, supported by a scanty connective tissue stroma. The solid portion of the tumour consists of rounded islets of epithelioid

cells lying in a vascular fibrous stroma. Around many of the epithelioid masses there is a distinct condensation of the connective tissue. The cells of the peripheral layer of the epithelioid islets are cylindroid; those more centrally placed are polygonal. In a considerable number of the epithelioid masses an oval or circular space is present surrounded by cubical cells radially arranged. Very few mitotic figures can be seen.

The appearances of this case were so interesting that a search was made through the records of ovarian tumours for the last nineteen years. All specimens of unusual character had been kept over that period. Six further cases were discovered, the histological appearances of which closely resembled those of the case quoted above.

We have tabulated the important features of these cases, as ascertained from the notes made at the time the patients were in the hospital.

The following is a brief summary of the cases:—

Case No.	Histological type of tumour	Age	History: Menopause	History: Bleeding	Operation	Period traced for
1	Cylindroid	48	Amenorrhœa several months	—	L. ovariotomy and L. salpingectomy	4 years
2	Cylindroid	34	5 years ago	+ slight	L. ovariotomy	6 years
3	Follicular and cylindroid	54	5 years ago	+ 1 year	Panhysterectomy and L. ovariotomy	10 years
4	Mosaic	34	Amenorrhœa 6 years	+ 8 months	L. ovariotomy	13 years
5	Follicular and cylindroid	23	Amenorrhœa 2 years	++ 3½ years	L. ovariotomy and resection of colon	11 years
6	Cylindroid	56	6 years ago	Blood-stained discharge	L. ovariotomy	15 years
7	Follicular	60	8 years ago	+ 4 months	Panhysterectomy and adnexa	11 mths.

Clinical history.—It will be noted that the age of the patients varies from 23 to 60 years. The tumours are therefore not confined to post-menopausal life.

The two most interesting points relating to the clinical history are the question of the degree of malignancy of the tumours and their effect on menstruation.

We have traced all these seven patients for periods varying from eleven months to fifteen years. With the exception of Case No. 2, all the patients have been seen by one of the surgeons at the hospital and are known to be alive and well at the present time. In Case No. 2 the patient was well six years after operation; her present address is not known.

The clinical notes—again with only one exception—describe in each case a period of amenorrhœa of several years' duration, followed by a period of irregular uterine hæmorrhage. In the older patients, the amenorrhœa was assumed to be physiological, but its occurrence in the younger patients is particularly interesting. The bleeding which occurred varied from a blood-stained discharge in one patient to a fairly severe hæmorrhage in others. In three cases it was the hæmorrhage, partly or solely, which caused the patient to consult a doctor.

In Case No. 1 the patient had no hæmorrhage. This case, however, is the only one of the series which was operated on as an abdominal emergency, torsion of the pedicle having occurred two days previously.

The operation performed in each case depended on the opinion of the surgeon as to the nature of the tumour. In two cases total hysterectomy and bilateral salpingo-oöphorectomy were performed, on the supposition that the tumour was malignant. In Case No. 5, oöphorectomy was combined with partial resection of the colon for a pedunculated lipoma, which was causing intussusception.

In four cases a little free fluid is reported as present in the peritoneal cavity; blood-stained fluid was present in the case with torsion of the pedicle. In no case was there any adhesion of the tumour to surrounding structures.

Pathological findings.—The naked-eye appearance and histological structure of all the tumours present many features in common.

The size of the tumours varies from about 10 in. by 8 in. by 7 in. to 4 in. by 3 in. by 3 in. The capsule is tough and fibrous and non-adherent to surrounding structures. On section, the tumour is partly cystic and partly solid. Bright yellow patches in the solid parts are often present, and in some of the specimens considerable hæmorrhage is found.

The macroscopic appearance of the tumour gives no idea of the large amount of epithelioid tissue found on microscopical examination.

The histological structure falls into three groups according to the predominating type of arrangement of the epithelioid cells. (1) The follicular type (fig. 1, p. 48) characterized by the presence of islets of epithelioid cells varying in size from that of a normal adult Graafian follicle to three or four times that size, is exemplified by the case (No. 7) described above. (2) In four cases of the present series, the epithelioid cells are arranged, for the most part, in strands or columns. The epithelioid cells abutting on the connective tissue stroma tend to be cubical or columnar, and spaces surrounded by radially arranged cubical cells are found, as in the follicular type. This variety may be termed cylindroid (fig. 2, p. 48). (3) The epithelioid cells in the third, or mosaic, type have a much less definite arrangement than in the first or second varieties. The strands of epithelium form an irregular pattern in a scanty connective tissue stroma (" moiréartig," R. Meyer).

Follicular or cylindroid structures, however, are present in some part of the tumour, making identification possible.

Literature.—An ovarian tumour of this type was first described by von Kahlden in 1895. Since then forty tumours have been reported, of which the histological structure is similar to that of von Kahlden's case and to that of the seven cases we have collected. The tumours are variously described as " carcinoma cylindratosum " (Isbruch, Neumann), " carcinoma folliculoides " (Meyer, Neumann), oöphoroma folliculare (Brenner, Te Linde), " folliculoma " (Gottschalk, Picard), " granulosal-cell tumour " (Te Linde, Neumann, Tietze), depending on the type of cell structure which preponderated, follicular in von Kahlden's case, cylindroid in many of the others (e.g., Te Linde's).

Te Linde, writing in 1930, tabulates the nomenclature, age and after-history in thirty-six cases which he had collected from the American and European literature, and gives a full description of four cases of his own.

Flemming describes " three cases of unusual ovarian tumours," which, in her opinion, are similar to, but not identical with, granulosal-cell tumours. Flemming and Te Linde give extensive references to the literature of the subject.

The histological structure of the tumours is fully described and illustrated by Robert Meyer and by Neumann.

Diagnosis.—The diagnosis of a case of granulosal-cell tumour depends essentially on the histological structure. It may be suggested at operation by the partly solid, partly cystic, structure, by the tough capsule, by the absence of adhesions, and by the appearance of brightish yellow patches on the cut surface.

The differential diagnosis from a fibroma with hyaline degeneration may only be possible on microscopical examination of sections from various parts of the growth.

The histological structure of secondary carcinoma of the ovary may present appearances somewhat similar to those of the granulosal-cell tumour. The differentiation depends on the larger size of the cell, the absence of radial arrangement, the deeper staining of the nuclei and the lesser density of the stroma found in the secondary carcinoma. The latter tumours are less likely to be cystic and tend to be bilateral.

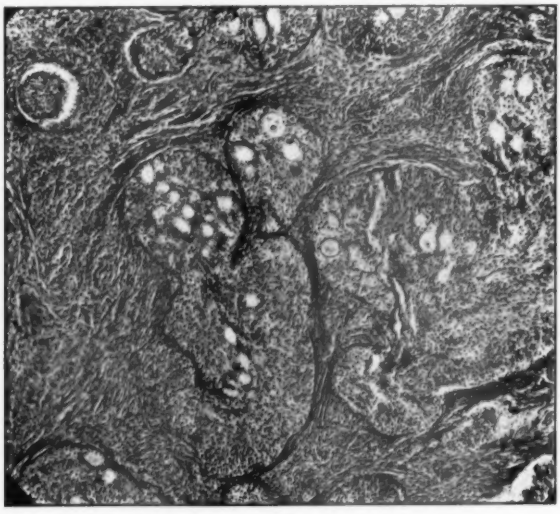

FIG. 1.

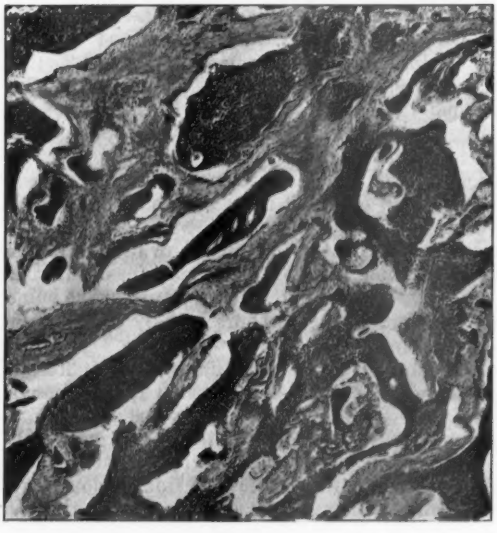

FIG. 2.

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Primary Adenocarcinoma of the Vagina.

By GILBERT I. STRACHAN, M.D., F.R.C.P., F.R.C.S.

PRIMARY cancer of the vagina is usually epitheliomatous and may arise anywhere in the vaginal wall; secondary carcinoma is also most commonly an epithelioma which extends by direct spread from a carcinoma of the cervix; it may be, less commonly, adenocarcinomatous, and is then usually secondary to carcinoma of the body of the uterus. A series of such cases was discussed by the writer in 1930.

Primary adenocarcinoma in this situation is, however, a rare condition, and it is for this reason that the two following cases are described and discussed.

Case I.—Mrs. E. S., aged 50. Carcinoma series No. 246. She was a multipara with eight children, the last born twelve years ago; two of the labours were instrumental, and there were no abortions. Eight years previously subtotal hysterectomy had been performed for a fibromyoma.

For a year she had suffered from vaginal discharge followed six months later by pelvic pain, while irregular vaginal hæmorrhage had occurred for the last three months. Loss of appetite had developed with constipation, while she had become thinner during the previous three months.

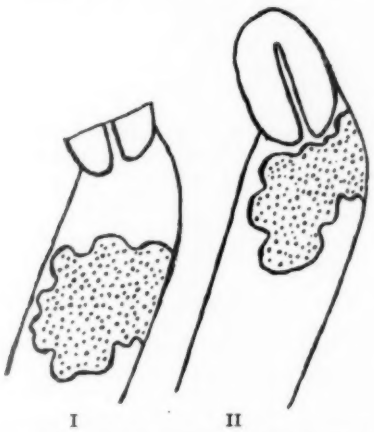

Diagram to indicate the position of the carcinoma in Cases I and II described in the text.

On examination, the general condition was fair. The vagina was fully occupied by a soft fungating friable growth, and as further investigation was not called for at this stage the condition was regarded as a cauliflower carcinoma developing from the stump of the cervix left at subtotal hysterectomy. Subsequent exploration under anæsthesia, however, showed the cervix to be eroded but not involved in the growth, which was now found to be arising from the posterior vaginal wall about its middle part. On digital manipulation the whole mass came away, and a curious feature of the case was that there was little or no resulting hæmorrhage, while the site of origin was left practically clear, with very little induration. A localized raw area was the only sign that any vaginal growth had ever been present.

Microscopical examination of the tumour—Section 5,381—showed typical adenocarcinoma. The appearance was of fairly rapid growth, so that, while definite acinous formation was frequently seen, irregular masses of carcinoma cells with only partial glandular formation were common. Mitotic figures were plentiful, and the stroma was scanty.

Seventy mgm. of radium were inserted, rolled up in gauze, into the vagina for twenty-four hours—1,680 mgm. el. hours—and under observation the symptoms disappeared and the

vagina remained clear for twelve months. Re-examination at this time, however, showed practically a reproduction of the condition as orginally seen; the growth was easily removed digitally as before; the same lack of local infiltration was present, and the microscopic picture was as previously described.

A stronger application of radium was now given—150 mgm. again wrapped in gauze and for forty-eight hours, 7,200 mgm. el. hours—and up to the present there has been no recurrence of the growth.

A few weeks ago—twenty months after first being seen—she came to hospital complaining of rectal hæmorrhage, and examination at this time showed some adhesive vaginitis but no clinical sign of return of the growth. The adhesions were broken down and the vagina canalized. Rectal examination showed an ulcer on the anterior wall; this was not indurated or surrounded by infiltration and was regarded as a radiation ulcer. On treatment by rectal lavage this condition is now rapidly clearing up.

Case II.—Mrs. T., aged 48 years. Carcinoma series No. 326. Nulliparous. For some reason which could not be ascertained, double oöphorectomy had been performed about twenty years ago.

The history was of vaginal hæmorrhage of five months' duration, worse on straining, with yellow discharge and low pelvic pain of similar duration. There was slight constipation, but there were no bladder symptoms, while the general condition was good and there was no loss of weight or asthenia.

Pelvic examination showed the vagina almost completely filled with a large, friable, fleshy mass which, under anæsthesia, was found to arise from the posterior vaginal wall just behind the cervix which itself was nulliparous and free, while the uterus was felt on exploration as a small mobile organ one inch and a half long.

As in the previous case, the tumour was easily removed digitally, leaving what looked like a sharply circumscribed hole in the vaginal mucosa of the posterior fornix. Bleeding from this area was slight, and again induration or infiltration was practically nil.

Microscopic section of the material removed—No. 6,836—showed clearly marked adenocarcinoma, the appearance of the section closely resembling that in the previous case.

Eighty-eight mgm. of radium in two bullets were inserted into the gap in the vaginal mucosa, and retained there by packing for thirty hours, thus giving 2,640 mgm. el. hrs. The result, so far, has been satisfactory, and on re-examination a few days ago only a puckered scar was found in the posterior fornix, with no bleeding or sign of recurrence, but as the case came under observation only four months ago, the ultimate reaction to treatment cannot as yet be judged.

It is generally admitted that primary cancer of the vagina is rare, and adenocarcinoma particularly rare, but it would seem fair to assume that the two cases reported represent examples of the latter condition. This assumption rests largely on the absence of any other obvious primary focus.

In the first case the indication for hysterectomy was stated to be a "simple tumour of the womb" and this was supported by the fact that the operation was subtotal. Again, the period of seven years between the hysterectomy and the onset of the present symptoms is so long that the present condition is unlikely to be associated with the previous uterine lesion, especially as the cervical stump, the most likely seat of recurrence if the condition were carcinomatous, is now unaffected. In the second case uterine carcinoma has been put out of court by exploration. As she was twenty-eight years of age when double oöphorectomy was performed, carcinoma of these organs is very unlikely and the condition calling for removal was probably inflammatory; again, the long period elapsing since the oöphorectomy is against the ovarian lesion having any causative effect on the later developing vaginal condition. As regards malignant metaplasia of a previously existing endometrioma of the recto-vaginal septum, this could hardly develop in the second case twenty years after oöphorectomy while, in the first case, the position of the carcinoma is in a site in which endometrioma is not found.

Of 328 cases of gynæcological carcinoma treated by the writers with radium since October, 1922, 267 have been carcinoma of the cervix, 36 carcinoma of the body of the uterus, 13 (including these two cases) primary carcinoma of the vagina, and 12

epithelioma of the vulva, and this incidence of primary vaginal carcinoma—3·9 % in general and 0·55% in the case of adenocarcinoma—is greater than in most similar series of cases.

Gurlt, Roger Williams, Schwarz, Hofmeier, Rhode and others, investigating the frequency of carcinoma of the vagina in large series of collected cases, have found that it occurs in about one in 1,500 cases of gynæcological carcinoma. When it is remembered that almost all of these are cases of epithelioma, it will be appreciated that primary adenocarcinoma in this region is excessively rare. On the other hand, Mary Moench, recently investigating 37 cases of primary carcinoma of the vagina in the Mayo Clinic, found two examples of adenocarcinoma. These were not definitely stated to be primary, however, and the possibility of their origin from a pre-existing endometrioma of the recto-vaginal septum is discussed.

In discussing the ætiology of the condition it has to be remembered that the vagina represents the lower third of the fused Müllerian ducts and, in its lower part, the urogenital sinus. The squamous epithelial lining contains no glands, although an occasional crypt-like depression may have a superficial resemblance to an acinus. In the fornices, however, glandular elements may be found, and these are considered by Veith, Höhne and Meyer to be misplaced intracervical glands. Again, the remains of Gärtner's duct—Wolffian—may be found in the antero-lateral vaginal wall, and this is lined with columnar or cuboidal epithelium.

It is also of importance to consider what factors, structural or otherwise, may produce or may predispose to the production of carcinoma of the vagina, and in this connection the prolonged wearing of a pessary and the irritation of a completely everted vagina in complete uterine prolapse have been quoted as causes, but neither was operative in the cases recorded. The relative frequency of the condition in the posterior vaginal wall has been explained by Frank as due to the accumulation of macerating discharges in this situation.

An intermediate and presumably pre-carcinomatous condition of the vaginal wall is found in the various cases of adenoma formation which have been reported in this situation from time to time.

As long ago as 1877 von Preuschen reported a condition of this kind where mucous secreting glands were found scattered throughout the vagina and opening on to the surface. In 1910 Bonney and Glendinning described a similar condition of diffuse adenomatosis of the vagina which they considered to be due to potential gland-forming powers possessed by the vaginal epithelium, and that this power had lain dormant until activated by an excitant. Immediately after this, in 1911, Haultain published a similar case which he had followed for fifteen years and which, finally, showed signs of transition to adenocarcinoma.

Herbert Spencer in 1923 described a condition of adenoma of the anterior vaginal fornix. The condition resembled carcinoma of the cervix at the first examination, but later it was found to be clear of the cervix and adenomatous.

From these considerations the origin of the adenocarcinoma in the cases reported does not appear to be Wolffian, as the structure was not merely columnar-celled but definitely adenocarcinomatous, and as they were both mid-line tumours and away from the lateral position of the Wolffian remnants. The most likely seat of origin, at least in the second case, would appear to be aberrant or heterotopic cervical glands which had become incorporated with the surrounding vaginal epithelium. The possibility of its origin being from an endometrioma, especially in the second case, has been discussed and dismissed. The means by which such heterotopic cervical epithelium becomes engrafted on the vagina and the causes which stimulate it to carcinomatous growth are not evident.

The clinical course of vaginal carcinoma is usually rapid and the thinness of the vaginal wall allows early extension to such adjacent organs as the rectum and bladder, so that radical operation is, in a large proportion of cases, out of the

question. Roger Williams puts the general expectation of life at about eighteen months.

Other recorded examples of primary adenocarcinoma of the vagina are not common; they usually have features similar to those reported in these cases, but Lövegren has reported a case of Ascheim's in which this condition was found on the anterior vaginal wall of a child aged six months.

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Section of Radiology.

President—Dr. J. M. Woodburn Morison.

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DISCUSSION ON CHOLECYSTOGRAPHY.

Dr. James F. Brailsford.

Abstract.—(1) No branch of radiology requires more careful attention to technique and detail than gall-bladder radiology.—(2) The X-ray examination should always include (*a*) a preliminary examination, (*b*) cholecystography, (*c*) barium meal, in this sequence.—(3) A number of gall-stones can be shown on the preliminary radiograph, and a further number on the cholecystograph, but there still remains a proportion which cannot be seen by X-ray examination. The greater the care taken in technique, the smaller will be the number of gall-stones not indicated.—(4) The radiographic demonstration of gall-stones does not necessarily mean that the lesion causing the patient's illness has been discovered. Gall-stones may exist without causing marked symptoms. They may produce symptoms which are atypical.—(5) The dye can be administered (i) by the mouth, (ii) intravenously. The former is now the best routine method of examination, though the latter still remains the more accurate.—(6) Non-filling of the gall-bladder in about 96% of cases indicates a pathological condition of the gall-bladder, often accompanied by stones, though these may not be shown on the radiograph.—(7) Poor filling of the gall-bladder on repeated examination also indicates a pathological condition of the gall-bladder. (8) A good gall-bladder shadow, which is normal in shape, size and position, uniform in outline and density, which contracts after a meal to a much smaller size, in a high percentage of cases indicates a normal gall-bladder. A small proportion of such gall-bladders may be diseased, and may even contain a small collection of stones.—(9) Any abnormality in the area of the gall-bladder before or after it has been filled with dye should be investigated by further radiographs taken according to the type of abnormality seen. (10) It has been demonstrated that a large collection of gall-stones in the gall-bladder can be passed into the intestine by way of the ducts.—(11) Complete gall-bladder radiology enables us to give a fairly accurate opinion as to the condition of the gall-bladder.

The medical profession owe much to Dr. Ewart Graham and his colleagues for introducing cholecystography. Prior to their researches, radiography of the gall-bladder was considered by many radiologists to be useless, though fortunately a few radiologists, by virtue of their excellent technique, their careful attention to details, their skill in manipulating X-ray plant having a very variable output, their knowledge of photographic technique and their keenness to help forward the progress of radiology, were able to obtain such success in the diagnosis of gall-bladder disease as to command the attention of all watchful clinicians. Among them stand out the names of Beck, Thurstan Holland, Robert Knox, Professors Haenisch and Köhler, Case, Cole, Pfahler, George, Leonard, and not least, Leo Rowden. A brief summary of the history of their work was given in a previous paper [1].

These men achieved their success because they were compelled to exercise

ingenuity and skill, and to pay attention to every detail in technique, from the preparation of the patient to the development and completion of the radiographic plate. They were sound clinicians and not mere photographers.

In no branch of radiology is careful attention to technique and interpretation more necessary to success, and the best results will be obtained when the radiologist himself carries through the whole technique.

If I were asked on what the value of the radiologist's opinion depends, I should say (1) the experience which enables him to take radiographs of good quality. (2) A knowledge of the technique of pathography and radiology. (3) Sufficient knowledge of pathology to enable him to visualize the lesion producing departure of the radiographic appearances from the normal, and the characters of the lesions likely to be seen in different diseases. (4) A sound knowledge of clinical medicine and surgery. This will guide him in the choice of the method of examination best likely to show the lesion and the cause for the clinical signs.

The radiologist's report concerns the evidence offered by the X-ray examination, on which the clinician should be able to rely, and should be so worded as to convey the radiologist's opinion of the nature of the pathological lesion revealed. A mere description of the radiographic appearances presupposes that the clinician can interpret the significance of shadows which he would probably not notice unless the radiologist pointed them out to him. The significance of radiographic appearances is best appreciated by those who make it their sole study; the subject is too vast to permit of excellence in any other specialist subject; even the regional specialist who attempts to interpret radiographs is usually ignorant of the fundamental radiographic technique and the changes in appearances due to alteration of that technique, also of the appearances familiar to the radiologist in other parts of the body—and this knowledge may be an important factor in the diagnosis of the case.

I remember the surprise of the medical officers at the War Hospital where I was stationed in 1915, when the bacteriologist repeatedly reported the finding of gas-forming organisms on foreign bodies, the radiographs of the limbs containing which I had previously demonstrated to them as showing gas bubbles in the soft tissues.

It is the duty of all radiologists to issue a report with every radiograph sent to the clinician, and it is on the value of his reports that his reputation should be built up. Wise clinicians realize this and, like ourselves, must be familiar with many instances of error due to inexperienced interpretation.

Preparation of the patient.—The gall-bladder is in close relation to the hepatic flexure and the first part of the transverse colon, the stomach and duodenum, and its shadow may be obscured by opaque or gaseous contents of these organs. If bismuth or any other opaque material has been taken by the patient, a mild aperient should be given two days before the X-ray examination and the patient kept on light diet during this period. Drastic purgatives are likely to result in distention of the bowel by gas which will obscure the gall-bladder shadows.

If the patient is constipated a simple enema may be given, followed by a saline enema to wash out the contents of the bowel, taking care that no air is introduced.

Preliminary radiography.—It is essential that before any opaque material is introduced into any organ for radiographic purposes, a preliminary radiograph should be taken and studied for any trace of abnormality. Failure to do so may result in faulty diagnosis and the missing of the essential lesion owing to the obscurity produced by the opaque medium used.

Radiography and subsequent surgery have proved that though the patient has what may be described as the clinical signs and symptoms of gall-bladder disease, the gall-bladder is functioning normally and is free from disease, an unsuspected lesion in another organ being revealed as the cause: also that gall-bladder disease may be accompanied by signs and symptoms which do not suggest any lesion of that organ, i.e. pseudo-angina.

In some cases of obscure abdominal disease the inclusion of a preliminary radiograph of the bones of the pelvis may throw useful light on the pathology of the condition.

The preliminary radiograph of the gall-bladder area I take with the patient lying prone on the Potter-Bucky diaphragm, with the arms folded above the head and the head resting on the left arm, looking towards the right, so that there is a slight rotation of the body to the right. The X-ray tube is centred 30 in. above the Potter-Bucky diaphragm over a point two inches to the right of the spine, over the last rib and an exposure given for from half a second to two seconds, varying with the thickness of the patient, using 100 ma. of current. The slight obliquity of the patient will throw the shadows of the gall-bladder away from those of the spine. Well-defined gall-stone shadows and a good shadow of a dye-filled gall-bladder may be entirely missed because they are superimposed on the shadows of the spinal column. It is obvious, therefore, that if thin gall-stone shadows are to be seen, these must be projected away from the shadows of the spine.

The shadows of well-defined, faceted calcium-containing gall-stones leave little to the imagination in interpretation. Examples of such radiographs are now to be found in practically every X-ray Department, though they were rare till a few years ago. The more common radiographic appearance is the ill-defined thin, flaky shadow which I believe can be demonstrated in about 30% of cases in which gall-stones are present. These shadows may be completely obliterated by the slight movement of the gall-bladder due to the body movement or visceral peristalsis, yet there may be little on the radiograph to suggest movement. They may only be seen on radiographs taken with a fraction of a second exposure, and can be best demonstrated by using a cone without the Potter-Bucky diaphragm. It is this type of shadow which the clinician finds it difficult to believe exists, even when its presence is indicated by the radiologist. Occasionally one finds that the wall of the gall-bladder is calcified and in some cases is full of opaque sand which produces a radiographic appearance similar to that of a dye-filled gall-bladder. This has led to the faulty interpretation of the cholecystograph in cases in which no preliminary radiograph had been made. In the case of solitary stones, difficulty of interpretation may be experienced but subsequent radiographs with alteration of position, and radiographs in different positions after the injection of the dye, will clear up most of the difficulties. The demonstration of gall-stone shadows on the radiograph does not necessarily account for the cause of the patient's illness, and if the complaint suggests any other lesion this should be searched for in addition. I recorded [3] the discovery of a small carcinoma of the transverse colon in such a patient over four years ago, and since its removal she has had no further symptoms.

Cholecystography.—There has been a gradual but marked improvement in the chemicals used in cholecystography. When I read my first paper on cholecystography in 1925 we were injecting sodium tetrabromphenolphthalein intravenously. This dye was toxic for a considerable number of patients, and the gall-bladder shadow compared with those now obtained was relatively faint. This dye was replaced by sodium tetraiodophenolphthalein because the latter could be given in smaller quantities with lessened reaction and greater density of shadow. Gradually the oral administration of the dye was introduced, and improved. At the beginning this was a poor substitute for the intravenous administration, but was used for various reasons, good or bad. In March 1928 [3] I published in the *British Medical Journal* a paper containing the evidence collected after 500 cholecystographies, in which I expressed the opinion that I regarded the intravenous method as the most accurate. Now after another four years, during which period cholecystography has become a routine procedure in the investigation of gall-bladder cases, I am still of that opinion, though I have also to acknowledge such a marked improvement in the quality and function of the dye now used for oral administration, that this falls little behind the

intravenous in its results. Ever since oral administration was introduced there have been opposing camps, one in support of the intravenous, the other in support of the oral method. Until the last two years the weight of opinion was with the intravenous method, but now the oral has strong support. The arguments in favour of the intravenous method are that a known amount of dye is administered into the circulation and the degree of concentration of the dye in the gall-bladder is not so confusing; the gall-bladder shadow is not obscured by the shadow cast by the dye in the intestine; the hepatic function test can be made at the same time; it can be given to the patient who has nausea of a degree which will not tolerate oral administration. Preferably the patient is kept under the control of a nursing staff until the radiographs are made. The oral method does not necessitate hospital or nursing-home attention, the patient can take the dye at home and come up next morning for radiography. The radiologist is saved the trouble and worry of an intravenous injection and its complications. The reactions to the dye are relatively slight or absent—in many patients no abnormal symptoms are detected and no cathartic action from the dye occurs; whereas in others the dye acts as a strong cathartic.

In the early days of oral administration the dye used often caused violent vomiting, but the present oral preparations rarely give rise to vomiting. It is amusing to see that, while boasting of the good shadow produced by oral administration, some authorities urge against the intravenous method that the gall-bladder is so dense that negative shadows may be obliterated if this method is used.

Intravenous Administration: *Technique.*—Having made the preliminary examination, an inspection of the antecubital fossæ is made and the arm selected which shows the most prominent veins. At about 9 p.m. the patient, lying in bed, has the arm cleaned up with spirit: a tourniquet is applied to the upper arm sufficient to cause distension of the veins and a syringe needle is thrust into the median basilic vein. Blood spurts out of the end of the needle until a connection is fixed into it from a 40-c.c. syringe barrel containing a few c.c. of sterile normal saline. The syringe is connected by means of a rubber tube containing a small glass connection near the needle end. The saline is allowed to flow into the vein, the tourniquet being taken off immediately the connection is made between the syringe and the needle. The flow of saline is slow, and when most of it has left the syringe with every indication that it has gone into the vein, 30 c.c. of a filtered sterile solution containing 3 grm. of sod. tetraiodophenolphthalein are poured down the side of the syringe barrel. If the flow ceases (and this appears to occur more frequently in those veins one would least expect to give rise to trouble, i.e., the large superficial veins which are readily entered and from which blood spurts out while the tourniquet is in position as from an artery) the piston of the syringe can be applied with gentle pressure until the whole of the dye has been injected. On the slightest indication that the dye is not going into the vein the injection is stopped.

No food or drink apart from sips of water are allowed. The patient is brought to the X-ray department at 9 a.m., 11 a.m., and 1 p.m. on the following day and radiographs are made of the gall-bladder area, using the same technique as for the preliminary examination. Unless the gall-bladder is visualized it is customary to use 15-in. by 12-in. films owing to the variable position of the gall-bladder. Any abnormal shadows or irregularity of the gall-bladder should be investigated by taking additional radiographs in different planes. Bubbles of gas in the intestine may simulate negative gall-stone shadows. After the sixteenth-hour radiograph has been taken the patient is given a barium meal made up with malted milk, a radioscopic examination is made of the stomach and duodenum, and the relation of the gall-bladder to these structures carefully observed. In a paper on gall-bladder radiography in the *Journal of the British Institute of Radiology* in 1927, I recorded [1] a non-filling of the gall-bladder in two cases in which the gall-bladder was normal but in which an ulcer of the stomach or duodenum had been found at operation.

This observation has since been made by a number of radiologists and its possibility should be borne in mind. Only last week such an event was brought to my notice. A patient had had a cholecystographic examination and the radiologist had reported that the gall-bladder had failed to fill, but as the symptoms did not suggest gall-bladder disease the patient was not operated upon. He died from the perforation of a chronic ulcer on the lesser curvature. This emphasizes the importance, which I have previously given in the records of a similar case, of following up the cholecystograph with a barium meal. No clinician can be certain whether it is the gall-bladder, or the stomach, or the duodenum which is diseased. The fact that the patient's symptoms suggest disease of the gall-bladder and yet the cholecystograph suggests a normal gall-bladder, is not sufficient evidence that organic disease is not present.

It might be suggested that, if necessary, the barium meal can be given at a later date. In one case in which I recorded that the gall-bladder showed normal appearances, the patient was brought back to hospital within a fortnight with a perforated duodenal ulcer from which he died. At the post-mortem, the cholecystographic findings of a normal gall-bladder were confirmed and the perforated ulcer shown. This case and the one reported above prove that while in some cases of ulcer the gall-bladder fails to fill with dye, this cannot be depended upon. Significant shadows may be seen in the gall-bladder area after the barium has been given which were not noticed before.

Oral administration.—The preparation which I am now using is that called opacol. It is stable, and not very unpleasant to take, rarely causes any sickness, is readily absorbed and gives a good contrasted shadow of the normal gall-bladder. It is of British make and less expensive than some of the other preparations.

Technique.—The patient is asked to come for a preliminary radiographic examination, after which he is given a bottle containing the opacol and is requested to have a fat-free meal, dry toast, or biscuits, and tea at 6 p.m. and the whole of the contents of the bottle at 8 p.m. in half a tumbler of water, followed by a further drink of water to remove the taste from the mouth. He is advised to go to bed just before 8 p.m. and to return for X-ray examination at 9 a.m. the following day, having taken no food or drink apart from sips of water since 6 p.m. the previous evening.

The same technique for radiography is adopted as that described above, and the barium meal is given after the seventeenth hour from taking the dye. A further radiograph is always taken three hours after the barium meal as this may give additional evidence on the condition of the gall-bladder, stomach or duodenum.

Reaction.—With the oral preparation, the only likely effect is that of purgation, though in many cases this is not observed. No reaction of a serious nature due to the dye has been recorded. The test is therefore safe and in a high percentage of cases—probably over 90%—it is accurate, particularly if the preliminary examination and the barium meal are used as part of the examination.

If the cholecystographic findings, using the oral method, are opposed to the clinical findings, further information may be gleaned by a second oral test or by intravenous administration of the dye.

[*A large collection of lantern slides was shown illustrating the various points in the paper*].

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Mr. Stanford Cade:

In the radiological department of Westminster Hospital 1,018 cholecystographies have been carried out since 1926. Of these, 512 were in cases of suspected biliary disease studied by means of X-rays, and bio-chemical investigations. Subsequently, 118 patients were operated on and the diagnosis confirmed histologically. The technique of cholecystography employed at Westminster Hospital varies somewhat from that described by Dr. Brailsford. Preparation consists of purgation forty-eight hours previous to injection, administration of alkalies the day before and restriction of protein food. Freshly prepared sodium tetraiodophenolphthalein is used. The injection is given at 9.30 a.m. and skiagrams are taken three, five, eight and twenty-four hours after injection. Although in the last two years oral administration of the dye has reached such a stage of reliability that the shadows obtained are as good as those after intravenous administration of the dye, in cases where no shadow is obtained the oral method cannot be relied upon to furnish definite conclusions as to the condition of the gall-bladder; the intravenous method therefore, in my opinion, remains the method of choice. It is entirely safe if the dye used is pure, the solution freshly prepared (used within two hours of preparation) and the injection given slowly. Skill and care in intravenous injection are essential, as extravasation of the dye into the cellular tissues is followed by necrosis in direct proportion to the amount of dye injected into the tissues.

In the interpretation of the skiagrams the main point is the presence or absence of a shadow. Absence of a shadow as a rule means a diseased gall-bladder, due in the vast majority of cases to non-patency of the cystic duct owing to some organic lesion. In some few cases it is due to a spasm of the cystic duct; no shadow was detected in a few cases in which the gall-bladder was subsequently found healthy and the lesion present was a duodenal ulcer. The information obtained from cholecystography is, however, much more important if the shadows obtained at stated periods, 3, 5, 8 and 24 hours after injection, are taken into consideration and compared as regards size, position and density. In the normal gall-bladder, the second skiagram is always denser and smaller in size. This diminution in size and increase in density conveys the useful information that the mucosa of the gall-bladder is healthy and is capable of concentrating the dye, also that the musculature is active, permitting of active contraction of the viscus. Under identical conditions as regards food and radiological technique, the rate of emptying is also of importance. Shadows still present twenty-four hours after injection are obtained only in gall-bladders which do not empty regularly at periodic intervals. Slow emptying, poor concentration, lack of power of contraction, indicate a condition of chronic cholecystitis, not necessarily infective, and in most cases non-calculous. The importance of cholecystography in such cases lies not only in the aid to diagnosis but in the information obtained in connection with non-operative treatment of cholecystitis. The *sine qua non* for medicinal treatment is patency of the cystic duct. If there is evidence of chronic cholecystitis, the response to medicinal treatment can be controlled by comparison of shadows obtained after two or three weeks' interval. Cholecystography permits of an intelligent and controlled non-surgical drainage of the gall-bladder by magnesium sulphate and peptone given by the mouth.

Taken in conjunction with estimation of the blood bilirubin and cholesterol and duodenal drainage by the Meltzer-Lyon method, it enables the clinician to form an estimate of the biliary health in cases of non-calculous cholecystitis, "strawberry gall-bladder," and ill-health from intoxication from a gall-bladder when extravesicular symptoms mask the true clinical picture.

As regards Dr. Brailsford's remark as to the necessity of a barium meal, we must of course appreciate that the usefulness of cholecystography is strictly limited to the

diagnosis of gall-bladder conditions. A normal gall-bladder shadow is no evidence of absence of disease elsewhere in the upper alimentary tract.

Dr. S. Cochrane Shanks:

Preparation of the patient.—The essential point in the preparation of the patient is to empty the colon of fæcal contents and gas, particularly of gas. Most of this gas is merely air swallowed by the patient, and is more marked in those confined to bed. Where possible, the patient should not be confined to bed.

For cholecystography.—I use a preparation similar to that outlined by Mr. Cade, with protein restriction and alkalinization by sodium bicarbonate.

Oral v. intravenous methods.—In the past I much preferred the intravenous method. With the oral method, when capsules of the dye were used, absorption from the intestine was so uncertain that absence of a gall-bladder shadow was of doubtful significance. With the introduction of the soluble acid dye, this objection has largely disapeared.

Now, in the majority of cholecystographic examinations with which I have to deal, the dye is given by the oral method. Added to the increased reliability of the oral method, is the increasing disinclination of clinicians to go to the trouble and possible risk of an intravenous injection where the other method is available. Parenthetically it is worth noting that if extravasation of the injection has occurred a radiogram of the elbow will enable one to give a prognosis as to the sequence of events. A drop the size of a pin-head outside the vein will cause a reaction, with erythema and œdema. One minim is sufficient to cause localized necrosis, and more will probably mean an eventual skin graft in the antecubital fossa.

Contra-indications.—Among these I should like to mention obstructive jaundice. If this is of any marked degree, one can foretell that no shadow will be present, no matter what the cause. In addition, also, to the test being useless, it is dangerous. Death has been recorded from acute pancreatitis in obstruction at the ampulla of Vater, and the retrograde passage of the dye along the duct of Wirsung.

In such conditions, therefore, as catarrhal jaundice, obstruction of the common or hepatic ducts, carcinoma of the head of the pancreas, and toxic or infective jaundice, I do not consider cholecystography justifiable. In some of these, as in acute liver atrophy, the method would not come into the diagnostic picture, but in others it is sometimes asked for. In other words, where the Van den Bergh test shows a frank direct positive reaction, cholecystography should not be used. Where the biliary excretion is deranged to any degree, it would seem on general principles wrong to flood the blood-stream with a toxic drug, the channel of excretion of which is out of action.

For these reasons also, I should hesitate to use the method in developed portal cirrhosis with ascites. In these cases no shadow is usually obtained, apart from any question of a lesion of the gall-bladder or cystic duct.

Technique.—I should like to emphasize the point made by Dr. Brailsford that the standard view should not be a true antero-posterior. Slight rotation to the right in the prone position is necessary to cast the shadow of the spine clear of the gall-bladder.

Dr. Brailsford's technique surprised me in one detail, that of using the intravenous injection on the evening before the examination. I should be interested to hear from him in his reply why he has departed from the usual practice in this respect: whether for convenience' sake, or because he obtained better results. Personally, I value the radiograms taken at four and eight hours, as an indication of the rate of concentration of the dye.

The preparation I use now is opacol. It, like shadocol, iodeikon and T.I.P. meal, which I have also used, gives satisfactory results.

Interpretation of results.—In the preliminary radiograms calcification of gall-

stones of the gall-bladder mucosa will be seen if present, but I am interested in the percentage of visible stones recorded by Dr. Brailsford. I have been quite unable even to approximate to his figure of 30%. From five to ten per cent. is nearer to my experience.

It is said that when a normal gall-bladder shadow is present, disease of the gall-bladder can be confidently excluded. I should like to add a word of caution here. Quite a considerable cholesterosis of the gall-bladder mucosa may exist without destroying the mucosal resorptive and concentrating functions. The response on the part of a "strawberry" gall-bladder may range from a normally dense shadow to none at all. An increase in the blood cholesterol content, say in the region of 250—300 mgm. per 100 c.c., may give a clue to the diagnosis here.

Apart from this condition, I think that the general statement holds true, and its degree of accuracy is high.

It is in the cases presenting by the oral method a faint gall-bladder shadow that difficulty in interpretation arises, it being doubtful whether defective intestinal absorption, defective hepatic excretion, or defective concentration by the gall-bladder is the cause. Consideration of the general clinical aspect of the case may exclude the second cause, i.e., the hepatic. A large collection of the dye in the right colon may suggest that intestinal absorption is at fault, while delay in the emptying of the gall-bladder after food may point to a lesion in the latter. In cases where these points give no guide, and where the clinical picture is equivocal, it is better to repeat the test with the intravenous method, when possible, before a laparotomy is performed.

In the vast majority of cases, absence of a gall-bladder shadow indicates frankly either a cholecystitis or an obstructed cystic duct. Rarely it happens that a gall-bladder which has given no shadow by cholecystography, even intravenously, is reported on the operating-table to be without macroscopic signs of disease. It is possible that such gall-bladders may be the site of interstitial lymphatic infection, causing lymphatic block and consequent failure in concentration. Here I stand open to correction and instruction by the clinicians. Rosenow and Wilkie have clearly demonstrated that such cases occur.

The demonstration in relief of transparent gall-stones in a gall-bladder which concentrates the dye normally is a commonplace, and requires no stressing. The case of the large, transparent solitaire, however, may present difficulty. This condition may be simulated closely by a bubble of gas in a haustral pocket of the hepatic flexure behind the gall-bladder. A series of radiograms, taken from varying angles, will easily differentiate between the two, but a single radiogram may be very deceptive. If the solitaire stone be large, and the gall-bladder be of the long, narrow, visceroptotic type, a local dilatation may occur round the stone, which is pathognomonic.

Dr. Brailsford, in reply,

said that he gave the dye in the evening because it was more convenient for the house men and nursing staff, the patient was quiet during the night, and the results, he considered, were better than when the injection was given in the morning—perhaps because of the quiet interval. He emphasized the importance of absolute stillness during the exposures with the most rapid technique in order to secure the detail of shadows possessing little contrast to the surrounding structures, and illustrated his points with radiographs. Radiographs taken after the barium meal in some instances gave a significance to shadows which might have been ignored. A faint outline of the gall-bladder might be shown on such radiographs, though the previous radiographs apparently gave no trace of gall-bladder filling. There was a distinct advantage in having six or eight radiographs of the gall-bladder area because it was not infrequent to find gall-stone shadows of little density on some of these but not on others.

The following cases and slides were shown :—

By Dr. CHARLES WROTH (for Dr. STANLEY MELVILLE).

(1) **A Case illustrating the Importance, when examining the Œsophagus, of seeing the Patient in the Recumbent, as well as the Erect, Position.**

The patient had been investigated previously, and no abnormality had been found when this precaution was omitted, but on re-examination a small diaphragmatic hernia was discovered, only seen filled in the supine position.

(2) **Skiagram of Cholecystography before the days of Gall-bladder Dye.**

Showing how, after an opaque meal, the barium had passed from the duodenal cap into the cystic duct and gall-bladder, and also along the hepatic ducts. The patient had had a severe attack resembling biliary colic two months previously, when presumably a stone had ulcerated through, leaving a fistula.

(3) **Skiagram of a Localized Pleural Effusion on the Left Side.**

This was between the lung and diaphragm, and showed as a semilunar shadow, running antero-posteriorly in the lateral film.

By Dr. CECIL BULL. **? Thymoma.**

A mediastinal tumour was diagnosed in 1930, and thought to be lymphadenoma. X-ray treatment in 1931 caused considerable shrinkage of the tumour.

FIG. 1.—Showing the tumour extending on both sides of and above the aortic arch.

February, 1932. Postero-anterior (stereoscopic) and lateral films show a tumour of the superior mediastinum between the sternum and trachea. (See figs. 1 and 2.)

FIG. 2.—Lateral view (with barium in the œsophagus) showing the tumour between trachea and manubrium sterni.

Mr. T. P. DUNHILL said that of the uncommon tumours of the mediastinum he had removed two lipomas and several dermoids, but he had not before seen a tumour having the clinical and X-ray features of this one. The symptoms were those of pressure on the veins; there were none of tracheal pressure; the tumour was fairly well defined, and might still be encapsuled, and he thought that it should be explored by splitting the sternum and an attempt made to remove it completely.

By Dr. PETER KERLEY (by permission of Mr. WILLIAM TURNER).

Interlobar Empyema without Chest Symptoms.

In May 1930 a woman aged 20 was admitted to Westminster Hospital with the diagnosis of acute appendicitis. She gave a history of frequent attacks of abdominal pain. On examination, definite tenderness was found in the right iliac fossa; temperature 100°; pulse 100. Laparotomy performed by Mr. William Turner; appendix removed. Pathological report on appendix: "Small quantity of pus in the lumen." Convalescence was normal, and patient was discharged cured.

In July 1930 she returned to the out-patient department again complaining of pain in the right iliac fossa. Lesion of right kidney was suspected, but pyelography showed no abnormality.

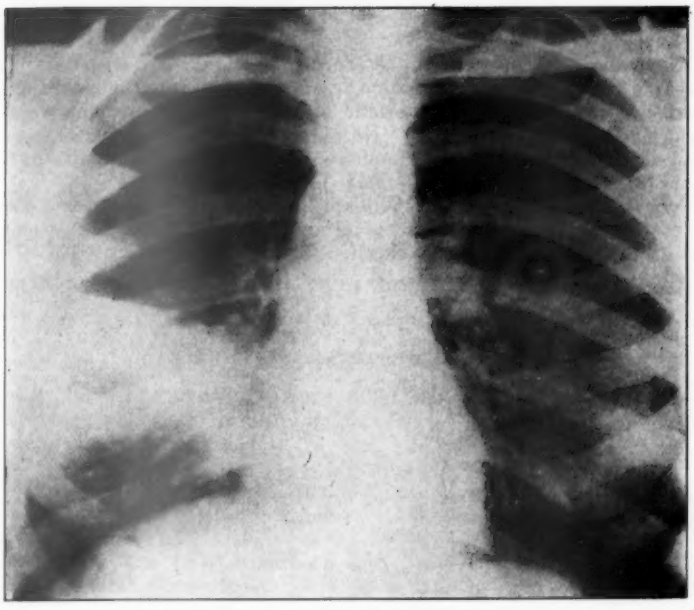


FIG. 1.—Interlobar empyema. Antero-posterior view.

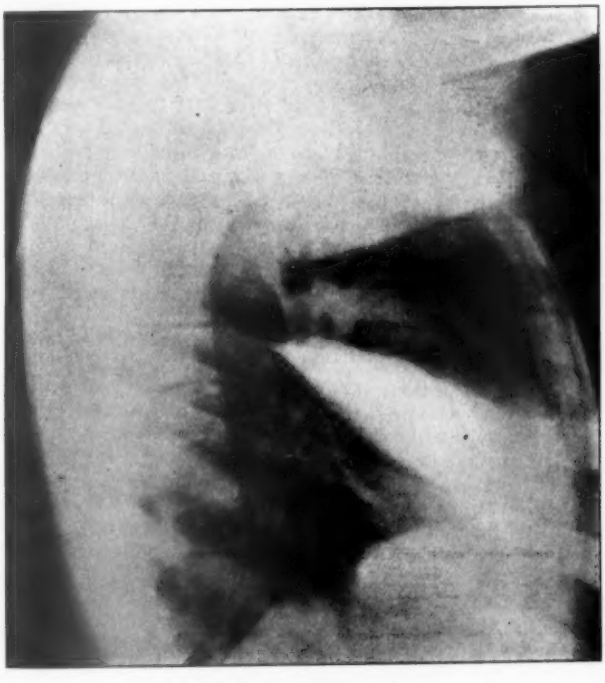


FIG. 2.—Interlobar empyema. Lateral view.

In November, 1931, the patient returned to hospital again with pain in the right iliac fossa. Barium meal examination; immediately before the meal the chest was screened and appearances characteristic of an interlobar empyema were found on the right side. (See figs. 1 and 2.) No symptoms referable to the chest; physical signs all negative. Barium meal examination revealed no abnormality of the gastro-intestinal tract.

The chest was opened by Mr. William Turner, and the empyema was drained. The organisms present were pneumococci and staphylococci. The patient made an uneventful recovery and is now in excellent health.

United Services Section.

President—Lt.-Col. E. M. COWELL, D.S.O., R.A.M.C. (T.A.).

[*March* 14, 1932.]

The Ætiology and Treatment of Heat Exhaustion and Heat Hyperpyrexia, with special reference to Experiences in Iraq.

By T. C. ST. C. MORTON, M.D., M.R.C.P., D.P.H.,
Squadron Leader, R.A.F.

I. *Climatology.*—The month of August, 1930, was characterized by a severe heat wave. The average shade temperature in Baghdad for the whole month was 114·4°. The peak was reached about August 5th and 6th, when for three days the shade temperature reached 120°.

In the Basrah-Shaibah area high temperatures were also recorded, the average daily shade temperature for the month being 115·3°, with a peak of 120° F. to 122° F. between August 5th and 8th, 1930.

Meteorological charts are appended for both the Baghdad and Shaibah districts, but figures for Basrah were not available; this latter is unfortunate in view of its notoriously high humidity, and the marked difference in the incidence of heat exhaustion and heat hyperpyrexia in the Baghdad and Basrah areas.

The summer of 1931 was one of the coolest on record for Iraq; the maximum recorded shade temperature for Hinaidi was only 115·9° F. on July 20th and in consequence only one severe case of heat hyperpyrexia occurred.

II. *Case incidence of effects of heat.*—Baghdad area. Twenty-seven cases (twenty-six airmen and onenursing sister) of heat exhaustion occurred at Hinaidi, and eighteen or 66·6% occurred on August 7th or 8th at a time when the shade temperature had persisted at 120° F. for three days. 62·9% of these cases occurred amongst personnel employed on sedentary occupations in offices, etc. In 48% of these cases there was no history of exposure to the sun, eight were teetotalers, and seventeen had not completed one hot season in Iraq. The main symptoms were vomiting (18 cases), dizziness (13), constipation (11), cramps (6), suppression of urine (4), anidrosis (3). Three cases of heat hyperpyrexia occurred, and in no case had there been any exposure to the sun.

Basrah area. Three cases of heat exhaustion and four cases of heat hyperpyrexia occurred.

III. *Ætiology.*—At Hinaidi our experience has shown that the critical temperature is somewhere in the region of 119-120° F., and that the factor of humidity does not appear to enter into the question to any marked extent, as the humidity percentage here remained low throughout. The large percentage of cases in which there is no history of exposure is suggestive, and points to the fact that a high temperature *per se* will bring about heat exhaustion and hyperpyrexia in susceptible subjects in the absence of direct exposure to the rays of the sun. The pathogenesis of these cases appears to be of the nature of an auto-intoxication due to the failure of the excretory organs to get rid of the products of metabolism. In heat exhaustion this is evidenced clinically by a prodromal period of malaise, weakness, constipation and diminution of urine. This stage persists for from one to three days, and is followed in severe cases by collapse. The patient shows all the signs and symptoms of profound shock; this may possibly be due to the presence of some substance allied to histamine, which has been produced in the body as a result of faulty

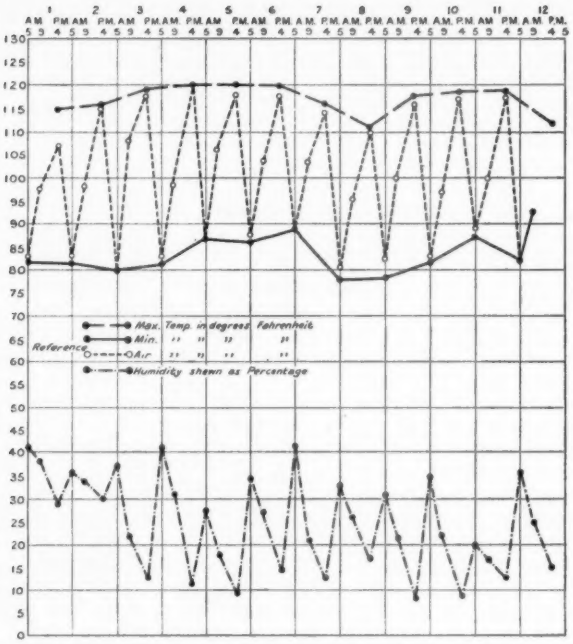


FIG. 1.—Maximum and minimum daily temperature and corresponding humidity at Hinaidi from August 1st to 12th, 1930.

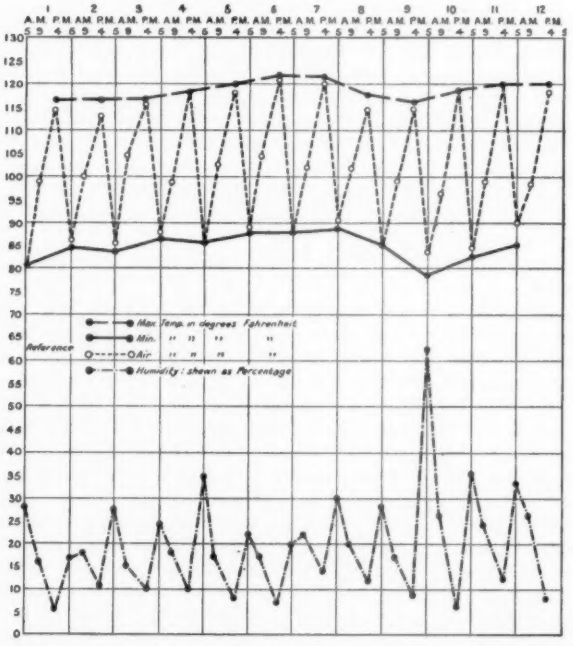


FIG. 2.—Maximum and minimum daily temperature and corresponding humidity at Shaibah, from August 1st to 12th, 1930.

(Royal Air Force Official. Crown Copyright Reserved.)

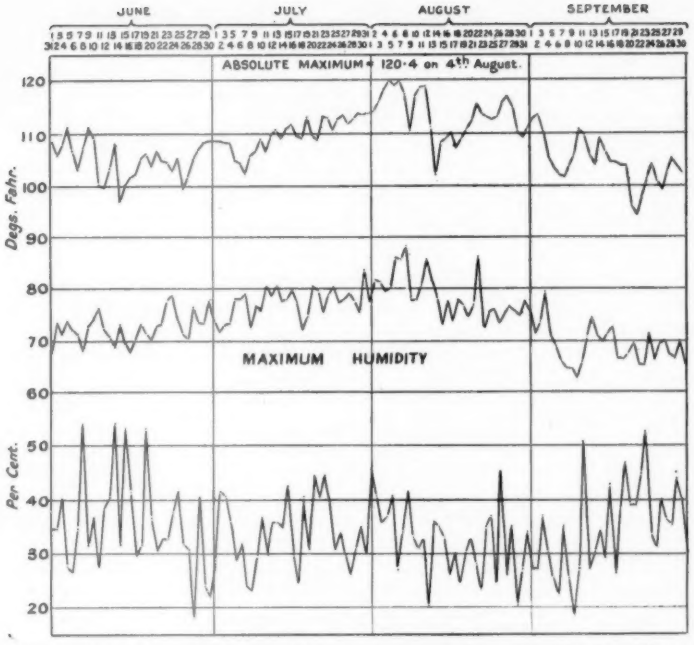


FIG. 3.—Maximum and minimum daily temperature and corresponding humidity at Hinaidi, from May 31st to September 30th, 1930.

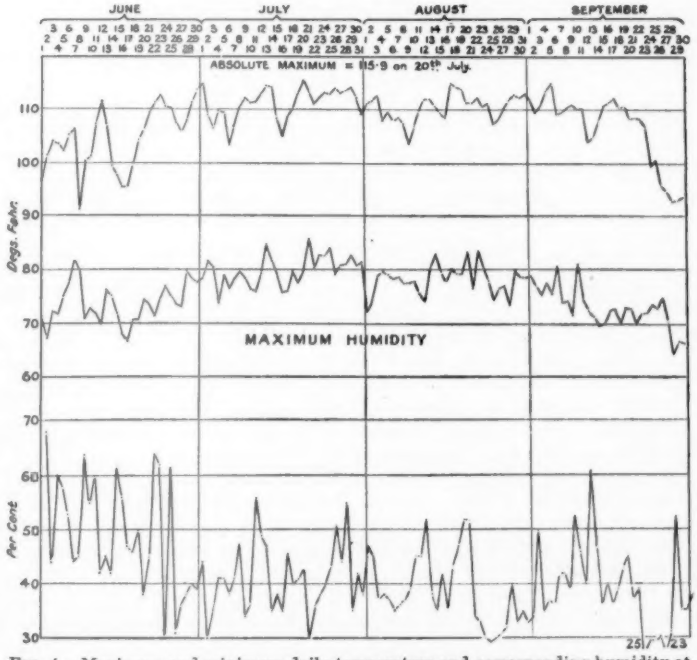


FIG. 4.—Maximum and minimum daily temperature and corresponding humidity at Hinaidi, from June 1st to September 30th, 1931.

(*Royal Air Force Official. Crown Copyright Reserved.*)

metabolism. The analogy to superficial burns is striking and suggests a similar pathology. In this connection Cramer's work on the production of heat hyperpyrexia in animals by the injection of β-tetrahydronaphthylamine is significant. The symptoms of shock gradually merge into a condition of acidosis.

The work of Hall and Wakefield on dogs, and the experience of Marsh in cases of heat stroke in the Persian Gulf, have shown that the following uniform changes occur in heat hyperpyrexia.

(*a*) There is a uniform increase in blood lactic acid. (*b*) The plasma carbon dioxide is reduced in consequence. (*c*) Twenty-four hours after the initial attack of hyperpyrexia, the blood urea increases probably on account of damage to renal parenchyma. (*d*) Diminution in man of blood chloride and urinary chlorides. This diminution is absent in non-sweating animals.

Willcox reports that in a few cases acetone and diacetic acid were present in the urine of cases of heat hyperpyrexia.

The abdominal and muscular cramp, which are such a distressing feature in many cases of heat exhaustion, yielded with dramatic suddenness to intravenous injections of sodium bicarbonate. These cramps are probably due to the accumulation of lactic acid in the system, and are possibly directly comparable to the muscular cramps that assail athletes after severe exercise,

Recent experiments on rabbits carried out by Dr. F. Marsh, of the Anglo-Persian Oil Company, have shown that, as long as the body is kept cool, the shaved head of a rabbit can be exposed to the direct rays of the tropical sun with impunity, although control animals invariably died from hyperpyrexia when this precaution was not taken. It is very suggestive that in the Hinaidi series of cases, as already stated, there was no history of exposure to direct sun-rays, and in both the Baghdad and Basrah areas all the heat hyperpyrexia cases occurred amongst men working indoors. This appears to point to the fact that it is the combined infra-red and yellow rays that do the damage, and not the ultra-violet rays.

Heat hyperpyrexia and heat exhaustion are due to general "parboiling" and not to any mysterious property in the rays of the sun. I have spent many hours bathing, bareheaded, in the height of the summer in Iraq with no ill effects, nor have I ever heard of any cases of hyperpyrexia arising in this manner. The solar topee is of value purely as a cooling agent, and the reason why bareheaded individuals are liable to suffer ill effects from exposure to the sun is simply due to the local parboiling of the blood in the brain raising the general temperature of the blood circulating in the body: this is true of healthy individuals in those already hyperthermic; as Sir Charles Martin has pointed out, there may be a direct heating effect on the brain itself. "Such a local addition of radiant energy to an already heated brain may be the explanation of cases of people who certainly were not sufficiently hyperthermic to be suffering from heat stroke, but yet became very ill with meningeal symptoms. Such cases are described in the literature. My interpretation of these cases is that they are due to a local parboiling, not to general hyperthermalism." This quotation provides, I think, the clue to the diversity of symptoms and syndromes in the literature which tend to obscure the clinical picture. There must have been during the war a high incidence of so-called "heat strokes" resulting from the effects of high atmospheric temperature and exposure to the sun, occurring amongst undiagnosed cases of malaria, sandfly fever, enterica and other toxæmias.

IV. *Nomenclature.*—There appears to be no hard-and-fast line between severe heat exhaustion and heat stroke. In fact it would be advisable to abolish the latter term and substitute the term heat hyperpyrexia in its place. Heat exhaustion cases of the severe acidosis type will, if untreated, pass on to heat hyperpyrexia, and once the rectal temperature reaches 108°F., in exhaustion cases, coma, convulsions, etc., ensue, and the clinical picture is altered to that of hyperpyrexia, although the essential pathology appears to be the same. In some of these cases the patients

developed heat hyperpyrexia without suffering from any of the symptons of heat exhaustion; this was probably due to an inherent instability of the heat centres in the individual concerned producing an early and initial anidrosis, but the disproportion between the incidence of heat exhaustion and hyperpyrexial cases in the Baghdad and Basrah areas points to a meteorological factor also being concerned. In my opinion the disproportion is due to the notoriously high humidity present at Basrah which tends to inhibit sweating. Unfortunately, no meteorological data for Basrah were available. What is often described as heat exhaustion is merely syncope.

V. *Epidemiology.*—It is well known that heat hyperpyrexia is especially prevalent in certain endemic zones. This is probably due to the fact that it is only in these zones that a constant high temperature is maintained over a period of time long enough to produce the metabolic changes that initiate the condition. The immunity in temperate zones from heat hyperpyrexia amongst furnace workers, stokers, etc., who in many instances are subjected to much higher temperatures than are found under natural conditions in the tropics, is due to the fact that they only work in short shifts. The break and return to a cooler atmosphere give their excretory organs ample opportunity of getting rid of the accumulated products of metabolism. That this is so is clearly shown by the experience gained by the medical officers of the Anglo-Persian Oil Company in southern Persia, where an artificially cooled ward kept at a temperature of 60° F. is used for the treatment of heat-exhaustion and heat-stroke cases; they report that cases admitted to this ward suffering from severe heat exhaustion—i.e., frequent vomiting, abdominal uneasiness, muscular cramps, diminution of urine, etc.—have often, within an hour, been relieved of all symptoms.

VI. *Heat exhaustion.*—(*a*) Clinical features. In most cases the actual onset was sudden, but there had been a premonitory stage, during which the patient complained of anorexia, weakness of the legs, headache and constipation, which lasted for three or four days, and was followed by sudden collapse in the severe cases. In many instances this collapse occurred at night and bore no relation to exertion. The patient in this stage showed all the symptoms of shock. As the immediate shock passed off, persistent and severe vomiting ensued, the vomitus eventually becoming bile-stained. The patient was pale, bathed in cold, clammy perspiration, mentally apprehensive, and in many cases in acute discomfort, due to violent cramps in the abdominal and leg muscles. Perspiration was, as a rule, profuse in this stage, but later on a certain proportion of the patients suffered from anidrosis. The urine was invariably diminished in quantity; in the severe cases there was retention and partial suppression, only 1½ to 2 oz. being drawn off in the twenty-four hours by catheter. An increase in the quantity of urine passed was always an early favourable sign of recovery. The axillary and mouth temperatures were often normal or subnormal, but the rectal temperature was invariably raised—usually to about 101° F. As the patient responded to treatment and the vomiting and cramps ceased, so *pari passu*, the mouth temperature rose, and a slight pyrexia appeared, which lasted for two or three days. In some cases headache persisted a week or ten days after convalescence was established.

(*b*) Mental changes. In one case, although there was no hyperpyrexia and the temperature was only 98·4° by mouth and 100·4° by rectum, there was maniacal delirium, and it was found necessary to anæsthetize the patient in order to administer an intravenous injection. Twelve hours later that patient was perfectly normal in every way.

(*c*) Pathology. Fortunately, no deaths occurred amongst the heat exhaustion series. Blood smears were taken in every case, and blood cultures and counts carried out in selected cases. One case of malignant tertian malaria was detected, and in another case, that of a nursing sister, although blood cultures were negative, persistent temperature led to further investigations being carried out, and *Bacillus*

typhosus was isolated from the stools on the tenth day, and from the blood during a relapse. Unfortunately, owing to the pressure of work, no estimations of blood urea or lactic acid, etc., were carried out during the epidemic; blood urea estimations have since been carried out on the severe cases before discharge from hospital, and no case of permanent renal damage has been detected, though in one case the blood urea was slightly raised one month after recovery.

(*d*) Treatment.—(1) Preliminary purgation and treatment for shock; (ii) the following mixture was given hourly for the first twenty-four hours: glucose, 1 drachm; sodium bicarbonate 15 gr.; water up to 1 oz. In certain cases where this was not well tolerated, potassium citrate 25 gr. was given instead. If neither of these was retained, from 1 to 1½ pints of 2% of sodium bicarbonate in saline was given intravenously. This was combined with 5% glucose in certain cases, apparently with benefit. The effect of the intravenous injection was dramatic, the vomiting ceased, the cramps in the muscles actually ceased in one instance whilst the transfusion was being carried out, and in every case within forty-eight hours the patient was practically convalescent. One transfusion sufficed in every instance.

VII.—*Heat hyperpyrexia.*—(*a*) Clinical features. There were seven cases of heat hyperpyrexia, three at Hinaidi and four in the Basrah area. (See Tables I and II.)

The striking point is that in no case was there any history of exposure to the direct rays of the sun. It is of interest that in the case that occurred in the R.A.F. General Hospital, Hinaidi, the temperature of the ward at the time reached 100° F., whilst the patient—a plethoric and alcoholic individual—was admitted suffering from sand-fly fever with a temperature of 103° F., and appeared to be on the verge of delirium tremens as evidenced by marked tremor, slurring of speech, restlessness and insomnia; he was therefore the worst possible subject.

(*b*) Therapeutic measures.—Great difficulty was experienced at the R.A.F. General Hospital, Hinaidi, in keeping the wards sufficiently cool. In spite of lavish supplies of ice and the free use of fans, it was difficult to keep the temperature below a minimum of 100° F. during the peak of the heat wave. This undoubtedly increased nursing difficulties and threw an extra strain on the patients. For example, in one case, for ten days the rectal temperature rose to 108° F. from one to three times in the twenty-four hours, entailing repeated ice sponging, ice enemata, etc. Ultimately a cool air chamber was devised by hanging sheets over his bed on cradles, and suspending ice in water-proof bags from the centre. The tunnel thus made was left open at both ends, and a large table fan at the patient's head blew cooled air through, keeping it at an even temperature of 89° F. By these means his temperature was kept between 99° F. and 102° F., and he ultimately recovered.

An artificially cooled ward kept at 60° F., such as that referred to (p. 23), would have been invaluable in the treatment of these cases. The treatment of this condition is to reduce the temperature as soon and as effectually as possible by the application of cold; iced enemata are not recommended as they interfere with the taking of the rectal temperature, and the rectal temperature affords the only certain index as to the moment to initiate therm-antidote measures. Intravenous injections of alkalies and glucose were disappointing in their results in these cases; in marked contradistinction to their striking success in heat exhaustion, their value in heat hyperpyrexia is prophylactic, not curative. The essential factor is the provision of a specially cooled ward. Profiting from our experience in 1930, attempts were made in 1931 to improvise artificial methods of cooling, and a considerable measure of success was finally achieved. The radiator of a Leyland lorry was kept filled with ice, and a fan drove air through this radiator by means of a tunnel into a small one-bedded bunk. By this means a constant temperature of 82° F. was obtained in this room at a time when the general ward temperature rose to 95° F. An opportunity arose in July, 1931, of testing the value of this ward. A severe case of heat hyperpyrexia was admitted.

TABLE I.—HEAT HYPERPYREXIA—ÆTIOLOGICAL FACTORS.

Case No.	Age	Time in Iraq in months	Nature and Conditions of Work	Habits—Alcohol	Exposure and Onset
1	23 years	22	In detention	Unknown	Had been 45 days under treatment for venereal disease in 1930, and 162 days similarly in 1929
2	38 years	22	Fire station	Heavy drinker. Plays no games	Admitted hospital 3.8.30 with typical sand-fly fever. Very fat, alcoholic. On 6.8.30 complained of pain in back. N.A.D. chest. Put on whiskey 1 oz. 4-hourly as delirium tremens was diagnosed. Marked tremor of tongue, jaw muscles and hands present. On 7.8.30 mental condition worse, whiskey increased to 8 oz. in 24 hours. Pot. bromide given. Temp. in ward was 100° F. in spite of fans and ice. On evening of 7.8.30 became delirious and temperature began to rise. At 20·00 hours temp. suddenly rose to 109·6° F.
3	33 years	10	Aircraft hand. Indoor work	States one bottle of beer a day. Swims and plays football	Admitted to hospital on 6.8.30 with rectal temp. of 104° F. Complaining of general pains and headache. Not perspiring
4	25 years	10	Clerk. Two fans in office, brick building with verandah	Beer. Two bottles a day. No games	No history of exposure. Had not been feeling well for a few days, suffering from diarrhœa. On 2.8.30 was admitted to S.S.Q. with headache. Temp. 103°. Eyes congested. On 3.8.30 at 14·00 hours became delirious. Temp. 107°. Pulse 140. Rectal temp. up to 112°.
5	23 years	10	Fitter A.E. Works in room with corrugated iron roof	Teetotal. Fences. Swims	No history of exposure. On 7.8.30 had been to Basrah on a trade test board. He reported sick on return, complaining of weakness, headache, dizziness. Temp. 100·4°. Pulse 88. Not constipated. On 9.8.30 rectal temp. rose to 107°.
6	48 years	13	W. and B.	Beer, three bottles a day. Had no alcohol for ten days previously	No history of exposure. Patient was admitted to hospital with furunculosis on 30.7.30. Developed heat hyperpyrexia. Temp. 109·6°.
7	23 years	22	Fitter. Armourer. Works in armoury workshop. Two fans in use. Brick building	Beer, two to three bottles a day. Cricket. Swims	No history of exposure. Had spent morning at a trade test board at Basrah on 8.8.30. Felt ill and returned at mid-day in an open touring car. Helmet and spine pad worn. Found in bungalow in a delirious condition. Transferred to sick quarters. Constipated.

TABLE II.—CLINICAL FACTORS.

Case No.	1	2	3	4	5	6	7
Date of admission	6.8.30	3.8.30	6.8.30	2.8.30	7.8.30	7.8.30	9.8.30
Prodromal malaise	+	+	+	+	+	+	+
Anidrosis	+	+	+	+	+	+	+
Constipation ...	—	—	+	—	—	—	+
Temp. on admission } mouth	—	103°	103°	103°	100·4°	—	—
Temp. on admission } rectal	—	—	104°	—	—	—	108°
Highest temperature recorded	—	109·6°	108·4°	112°	107°	109°	108°
Delirium	—	+	+ +	+	—	+	—
Coma	+	+	+	+	—	+	+
Convulsions ...	—	+	—	+	—	+	—
Pupils	—	Dilated	Dilated	Dilated	—	—	—
Tongue furred ...	—	+	+	—	—	—	—
Vomiting	+	+	+	+	—	—	—
Suppression of urine	—	—	—	—	—	—	—
Incontinence ...	—	+	+	—	—	—	—
Duration of fever	—	4 days. (Sand-fly fever concurrently)	—	—	3 days	8 days	3 days
Results and remarks	Died suddenly in S. S. Q. after removal from prison	Died. Case arose whilst patient was in hospital. Complicated by alcoholism	Recovered after prolonged treatment and many relapses. Very satisfactory case	Recovered. Very satisfactory case	Recovered	Recovered. Case arose whilst patient was in hospital	Recovered.

Patient was a non-commissioned officer, aged 38, who had served in Iraq for twenty-seven months. He worked as a storekeeper in an indoor job. His working hours were from 7 to 12 a.m., and he had taken no exercise for the last year. He drank about eight pints of heavy English beer a day. On July 29, 1931, he noticed some abdominal uneasiness, and had been feeling off colour for two from to three days. On July 30 he vomited three or four times, and noticed some frequency of micturition. He reported sick, and was admitted to hospital in a collapsed state the same day.

Condition on admission..—A fat, plethoric alcoholic. Face congested, pupils contracted, breathing stertorous, skin dry and hot, knee- and ankle-jerks absent. Heart, lungs and abdomen normal. Blood-pressure, 180/90. Mouth temperature, 104·8° F. Rectal temperature, 107° F.

The patient was ice-sponged, and his temperature fell to 104° by mouth and 105° per rectum. He was given a magnesium sulphate enema with excellent results, and was placed on sodium bicarbonate 10 gr., and glucose by mouth hourly. Unfortunately, owing to a mistake, a specimen of urine was not saved for examination. Blood-films were taken, and were negative for malaria. Blood-culture taken.

31.7.31. Improved considerably. Mouth temperature, 103°. Rectal temperature, 104°. Urine alkaline. Sodium bicarbonate and glucose mixture four times in the twenty-four hours. Blood-film negative for malaria.

1.8.31. Much better. Temperature: mouth, 101°; rectal, 102·5°. Blood-pressure, 145/90. Marked incoördination of hands. Knee- and ankle-jerks still absent. No sensory changes. Urinary chlorides, 0·29%. Nothing else abnormal.

2.8.31. Temperature: Mouth, 100·8°; rectal, 101°·5.

Blood-count.—Total white cells, 7,800. *Differential count.*—Small monos., 10%; large monos., 6½%; transitionals, 13½%; polys., 68½%; eosinos., 1½%. Blood-urea, 35 mgm. per 100 c.c. Foot-drop and wrist-drop developed. Case diagnosed as alcoholic peripheral neuritis. Splints put on.

3.8.31. Much improved. Temperature, 99° F. Urinary chlorides 0·06%. Blood-culture sterile.

6.8.31. Urinary chlorides, 0·8%. Temperature has remained normal for the last twenty-four hours.

The patient was sent home on 22.8.31, the extensors of his hands and right foot being still paralysed.

Prevention of heat hyperpyrexia in fever cases in hospital.—(1) Provision of an artificially cooled ward. (2) Potassium citrate lemonade made by adding from 10 to 15 grains of potassium citrate to a glass of home-made lemonade. A pint of this was given three times a day to all pyrexial cases.

This scheme was adopted early in the summer as it was found that the urine in many sand-fly fever cases was intensely acid, full of albumin and containing casts and red blood-corpuscles.

The lemonade was given as a routine in every case of pyrexia during the very hot weather and proved of considerable value. In my opinion it is worth advocating as a prophylactic measure for healthy people during a heat wave.

Estimation of urinary chlorides.—Dr. F. Marsh observed a diminution of urinary chlorides in a case of heat hyperpyrexia (*Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1930, p. 257). This diminution occurred in the case reported above, but unfortunately no further opportunity arose in 1931 to confirm it. In order to obtain standard figures for healthy people in the tropics as to the amount of chlorides normally present in the urine, daily observations were carried out on three laboratory assistants during the month of August, 1931, when the average shade temperature was 110°. The assistants were employed in sedentary indoor work. An elaborate table was exhibited showing the daily observations of which the following is a synopsis. The average of fluids ingested during the twenty-four hours was 3,672 c.c. (approximately 129 oz.), and in the same period 737·9 c.c. (approximately 26 oz.) of urine was passed with a chloride percentage of 1·07, or 7·8 grm. in the twenty-four hours. In temperate climates 1,450 c.c. (approximately 50 oz.) of urine is passed in the twenty-four hours with a

chloride percentage of 1, or 15 grm. In hot weather, therefore, according to this test, only about half the quantity of chlorides is passed in the urine, although the percentage remains practically the same.

(*c*) *Pathology.*—(i) Post-mortem (two cases).—The meninges and brain substance were markedly congested and hyperæmic. The heart was found contracted and stony hard, and the blood was very fluid. Smears taken from the brain, spleen and blood were all negative for malaria. Apart from the above, nothing abnormal was found except in the case of the N.C.O. whose heart showed an advanced fatty change.

(ii) Blood changes.—In one very severe case of heat hyperpyrexia repeated examinations were carried out during the course of the fever; an interesting feature was the leucocytosis and marked polymorphonuclear increase. No underlying disease could be found to account for these blood changes, and on looking up the records a similar finding occurred in a fatal case of heat hyperpyrexia during the 1926 group of cases. The following are the differential blood counts:—

Total white cells per c.mm.—24,000 (9.8.30), 18,000 (11.8.30), and 8,200 (12.8.30).

Differential count:—

	9.8.30.	12.2.31.
Small mononuclears ...	8% ...	15%
Large " ...	4% ...	10%
Transitionals	3·5% ...	4%
Polymorphs	83% ...	70%
Eosinophils	1·5% ...	1%

A blood-urea examination in this case carried out one month after the illness showed a slight increase (45 mg. of urea per 100 c.c.).

Prophylaxis during hot weather. (1) Dietary.—There is no doubt that the diet of the British other ranks during the hot weather in the tropics is physiologically unsound. I am convinced that the relative immunity to the effects of heat amongst Indian troops is due, to a considerable extent, to dietetic factors. The B.O.R. will insist on getting his rations, a ration eminently suitable for hard manual work in a temperate climate, a diet too rich in proteins and fat and much too poor in carbohydrates for the tropics. Custom has ordained that the main meal is eaten in the heat of the day instead of in the cool of the evening; some day this will be altered, but—not in our time.

The universal popularity of salted almonds, chip potatoes, etc., in the tropics is due to a natural craving to make good the salt deficiency resulting from excessive sweating, the obvious conclusion is greatly to increase the salt content in the diet. Alkalies are normally present in vegetables; where these are not procurable, the ingestion of small quantities of sodium and potassium citrate added to lemon drinks is advisable.

(2) Fluids.—It is unfortunate that the normal brands of beer supplied in the tropics are so heavy. Canteens should be forbidden to supply alcoholic refreshment until six p.m.; fresh lemon and orange drinks should be supplied at reduced charges to the troops. Well-diluted whisky-and-soda appears to me to be the best alcoholic drink in the tropics, and I have often considered it unfortunate that the B.O.R. is restricted to beer, a notoriously unsuitable beverage in hot weather. Men should be warned that relatively enormous quantities of fluid are necessary after exercise in the tropics; I have a conviction that perhaps due to the windy insufficiencies that masquerade as teetotal drinks, most teetotalers and women do not drink enough fluid to make good tissue loss, and that perhaps is the reason why so many of them crack up in hot weather; on the other hand, there is no doubt whatsoever that the chronic alcoholic is very prone to go down with heat hyperpyrexia, but this is due to two factors, namely, the ingestion of alcohol during the heat of the day and defective excretion of products of metabolism due to diseased liver and kidneys.

(3) Exercise.—Daily regular exercise is essential and helps to tone up the whole excretory system. Newcomers are rather apt to over-exercise at first; it is a wise rule to lay down a certain standard suitable to one's individual needs, for example, three sets of singles at tennis, and adhere rigidly to this, no matter how much one may be tempted by the competitive spirit to continue the game.

(4) Shade temperature and work.—Apparently a shade temperature of 120° F. persisting for more than three days, is the essential factor in the production of an epidemic of heat exhaustion and hyperpyrexia as far as Iraq is concerned. Such heat waves are exceptional and usually only occur at rare intervals; I therefore strongly recommend that all routine work be suspended as far as possible during such a period, and that emergency measures in the provision of extra ice, etc., be adopted to deal with the situation. By meteorological observation similar critical temperatures can doubtless be obtained for all tropical stations and the necessary precautionary measures be adopted. Until, however, artificially cooled wards are provided for serious medical and surgical cases in every tropical hospital, the spectre of heat hyperpyrexia will hang like a nimbus over the head of the operating surgeon, physician and patient.

In conclusion, I would like to express my thanks to Group Captain A. V. J. Richardson, O.B.E., Principal Medical Officer, Royal Air Force, Iraq in 1930, for his valuable criticism, advice and assistance in the preparation of this paper, and to my colleagues of the Royal Air Force Medical Service for their cordial co-operation, loyal assistance and helpful suggestions in the treatment of these cases.

Section of Otology.

President—Mr. NORMAN PATTERSON, F.R.C.S.

[*March* 4, 1932.]

A Case of Acusticus Tumour in which both Auditory Nerves were Involved by Separate Growths.

By ADRIAN DE KLEJN (Utrecht) and ALBERT A. GRAY.

I.—Dr. A. DE KLEJN (*Clinical Report*).

THE patient was a man, aged 28 in 1917, when the first symptoms appeared, consisting of cerebral disturbances associated with slight pareses such as difficulty in walking.

First otological examination (July, 1919).—Patient found to be quite deaf in the left ear; in the right ear there was partial deafness due to labyrinthine disease. Schwabach test, shortened. Rinne, positive.

Right ear.	*Left ear.*
Low tones 20 v.d. heard.	16 to 40 v.d. not heard.
Middle C a little shortened.	Not heard.
C_3 (normal 43 secs.) 31 secs.	Not heard.
Fis_4 (normal 29 secs.) 15 secs.	Not heard.
Upper tones G_6 heard.	No notes of Galton's whistle heard.

No deviation by Bárány test. Horizontal nystagmus on looking to the left, but only beginning when the eyes were turned 60 degrees or more to left of central line of vision. On looking to right there was a nystagmus to the right which began when the eyes were deviated more than 5 degrees from the central line of vision.

Caloric stimulation to left ear had no influence at all on spontaneous nystagmus, and produced no nystagmus on looking straight forward, but on looking to the right there was spontaneous nystagmus. There was no deviation during caloric stimulation to the left ear.

Caloric stimulation to the right ear produced typical nystagmus on looking straight forward, and also increase of spontaneous nystagmus on looking to the left. There was typical deviation of both arms (past pointing).

Clinical summary.—There was no response either to the tests for hearing or to the vestibular functions in the left ear. There was a considerable degree of nerve-deafesss in the right ear. The vestibular responses were to a certain extent active in the right ear.

X-ray examination of both petrosal bones by Stenver's method, showed that there was erosion of bone in the regions of both internal auditory meatus.

Numerous tumours were present in the skin of the back and of the right arm.

Second otological examination (February 27, 1920).—Erosion of the petrosal bones was now much more striking. In the right ear the patient could hear conversational voice at a distance of only one inch from the ear. There was no response to the vestibular tests in either ear.

Third otological examination (July 12, 1923).—The patient was quite deaf in both ears, and there was no response to the vestibular tests in either ear. There were no compensatory eye positions on either side, and the patient was almost completely blind.

The patient died in April, 1929, aged 40.

Post-mortem examination revealed typical Recklinghausen's disease of the brain. There were tumours in the retina and other regions of the body, but the description of this aspect of the case will be published by Dr. Nieuwenhuyse.

II.—Dr. A. A. GRAY (*Pathological Report*).

Pathological examination of the temporal bones. Right ear. Macroscopic appearances.—The posterior surface of the petrous portion of the right temporal bone that lies internal to the saccus endolymphaticus is eroded and replaced by tumour tissue. In the upper portion this tissue extends almost to the upper surface of the temporal bone. The walls of the internal auditory meatus are completely destroyed, and there is no trace of the seventh and eighth nerves. In the innermost portion of the petrous bone the tumour has eroded the bone as far forward as the carotid canal.

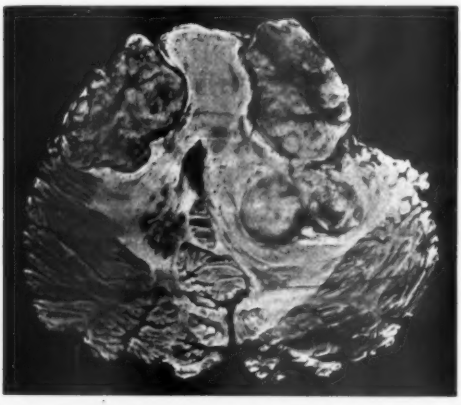


FIG. 1.—Showing portions of the growths on each side of the medulla which were removed along with the brain.

FIG. 2.—Right ear. *t*, *t*, tumour tissue; *n*, tumour tissue in vestibule; *s*, saccule; *h*, horizontal canal. (× 4.)

There is no sign of the growth in the middle ear, and this cavity is normal in appearance.

Microscopic examination.—The temporal bone was decalcified and sections were made in the usual way. The staining was done by hæmatoxylin and eosin. The sections were cut approximately in the horizontal plane, and from above downwards. Sections of the upper portion of the bone show great destruction of the internal portion of the petrous bone (fig. 2).

The growth has extended along the horizontal portion of the facial canal and has destroyed the facial nerve. The vestibule has been invaded by the growth, which forms a small oval mass in the saccule. This oval mass of tumour tissue lies

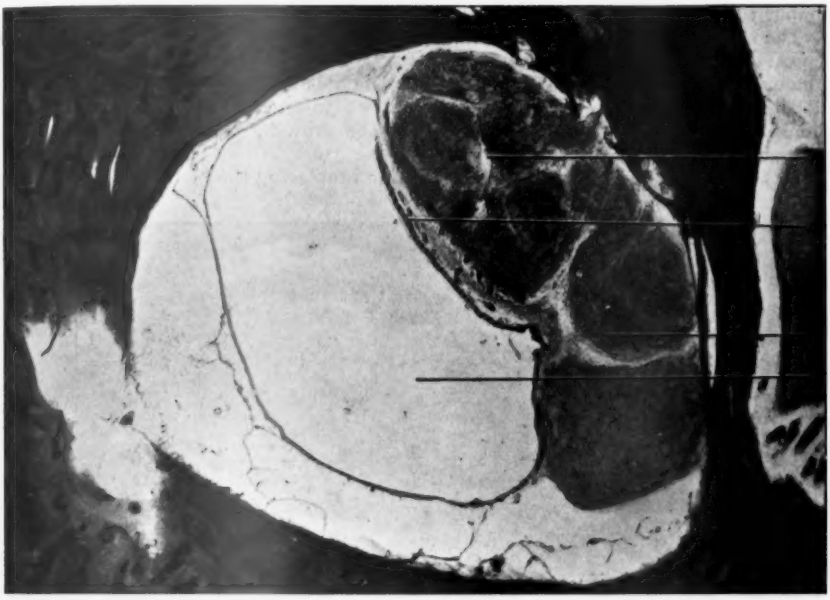


FIG. 3.—Right ear. *s*, saccule; *m*, macula sacculi; *n*, *n*, tumour tissue. (16 mm. obj., No. 1 eyepiece.)

FIG. 4.—Right ear. *f*, facial nerve; *p*, posterior canal; *t*, tumour tissue in cochlea; *s*, tumour tissue in vestibule; *m*, tumour tissue, main growth. (× 4.)

between the bony wall of the saccule and the endosteum, which has been raised up, bearing with it the macula sacculi. It is interesting to note that the neuro-epithelial cells of the macula sacculi are in no way destroyed (fig. 3), and preserve an unbroken

surface in spite of the fact that they have been pushed so far forwards into the cavity of the saccule. Sections lower down and passing through the stapes and cochlea show the semicircular canals and vestibule to be free of the growth, except in the small area in the saccule which is occupied by the lower portion of the mass of tumour tissue just described.

The stapes is free and not affected by the growth. The bony wall of the cochlea is not eroded by the tumour, but the cavity of the cochlea itself is invaded, the tumour tissue having advanced through the modiolus (fig. 4).

The portion of the petrous bone which lies internal to the cochlea has been almost entirely destroyed and replaced by the growth, which at one point lies contiguous with the carotid canal.

In the cochlea (fig. 5) tumour tissue is found replacing the bone of the modiolus

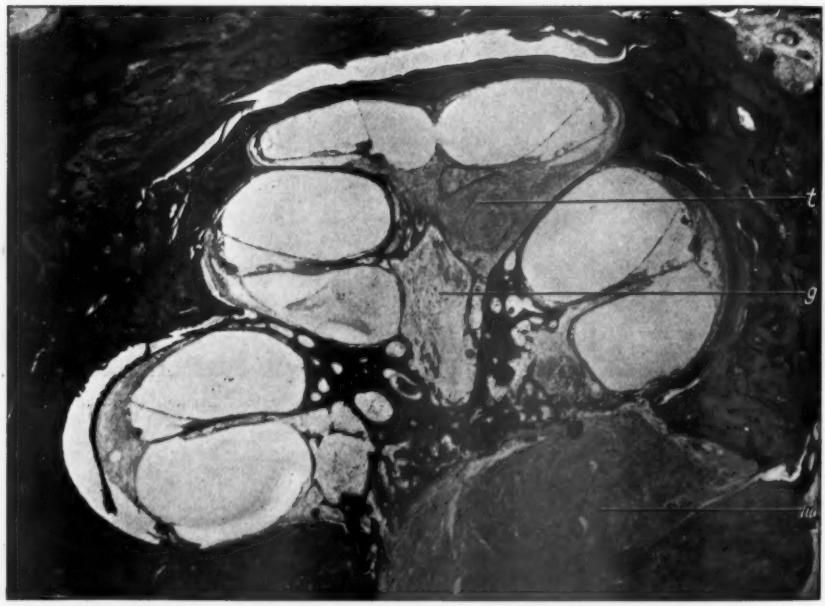


FIG. 5.—Right ear. *t*, tumour tissue in upper part of modiolus; *g*, ganglion spirali; *m*, tumour tissue in meatus. (× 20.)

in the upper region of the basal whorl, and another and larger deposit of tumour tissue is seen in the upper parts of the middle whorl and in the apical whorl; indeed, in this region the bony tissue of the modiolus has almostly completely disappeared. A small deposit of tumour tissue is found in the scala tympani of the middle whorl, but otherwise the cochlear passages are free of the growth. The membrane of Reissner is in its normal position throughout the whole of its course.

Examination of the cochlea under rather higher magnification shows interesting changes in the stria vascularis. This structure has undergone a process of vacuolization throughout its whole course, and the cylindrical or barrel-shaped cells which normally line its surface have entirely disappeared (figs. 6, 7 and 8).

In the apical whorl (fig. 8) the superficial portion of the stria vascularis appears to have been loosened from the underlying portion by the accumulation of fluid

underneath, and to be floating outwards into the ductus cochlearis. It is interesting to observe that a similar condition has been found in the cochlea of deaf-mutes by the present writer as well as by other investigators. And it is still more interesting to note that in these deaf-mutes this change is also found most pronounced in the apical whorl.

The organ of Corti in the apical and middle whorls and in the upper part of the basal whorls does not show any appearance which can be described as pathological (figs. 5, 7 and 8).

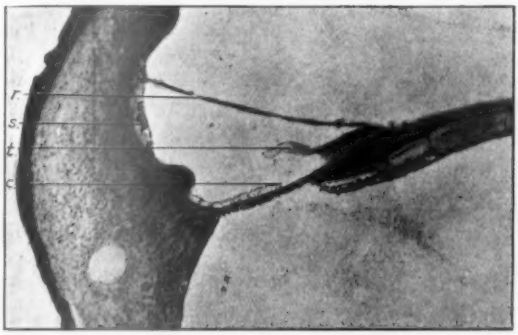


FIG. 6.—Right ear, lowest whorl. *r*, Membrane of Reissner; *s*, stria vascularis; *t*, tectorial membrane; *c*, place occupied by organ of Corti before it disappeared. (Zeiss 16 mm. obj. No. 4 eyepiece.)

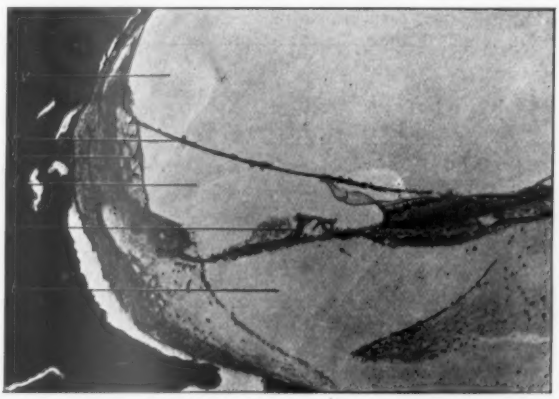


FIG. 7.—Right ear, middle whorl. *s,v*, scala vestibuli; *r*, membrane of Reissner; *h*, stria vascularis; *d*, ductus cochlearis; *c*, organ of Corti; *t*, scala tympani. (Zeiss 16 mm. obj. No. 4 eyepiece.)

There is a considerable degree of disintegration among the hair cells, but this is in all probability a post-mortem change since similar changes are found in the same structures in the human subject in individuals whose hearing has been normal during life.

The rods of Corti are present in the whorls mentioned above. In the lowest part of the basal whorl, on the other hand, a striking change is seen; for it is found that the organ of Corti has disappeared altogether (figs. 6 and 9). In this region the

cubical cells lining the outer portion of the upper surface of the basilar membrane are present, but at the point at which they normally give place to the cells of Hensen, the latter are not to be found; and the same is true of the outer rows of hair cells, the cells of Deiters, the rods of Corti and the inner row of hair cells. In this region, therefore, the basilar membrane, uncovered by the organ of Corti, lies bare to the

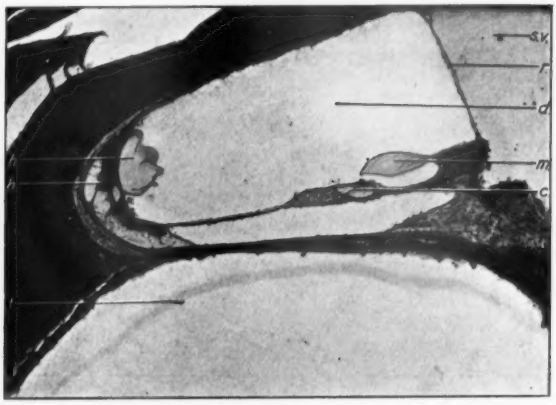


FIG. 8.—Right ear, apical whorl. *h*, *h*, stria vascularis; *t*, scala tympani; *s*,*v*, scala vestibuli; *r*, membrane of Reissner; *d*, scala vestibuli; *m*, tectorial membrane; *c*, organ of Corti. (Zeiss 16 mm. obj., No. 4 eyepiece.)

FIG. 9.—Portion of lowest whorl of cochlea; *s*, stria vascularis; *l*, ligamentum spirale; *r*, membrane of Reissner; *t*, tectorial membrane; *c*, position formerly occupied by organ of Corti. (Zeiss 16 mm. obj., No. 8 eyepiece.)

endolymph. There is no fibrous tissue or other structure to show where the organ of Corti formerly existed. It has simply disappeared without leaving any trace of its existence.

The tectorial membrane shows a normal appearance in all parts of the cochlear canal, even in that portion from which the organ of Corti has disappeared.

The ganglion spirale has been affected in a rather remarkable way (fig. 10). In certain regions such as the upper portion of the middle whorl, and the apical whorl, it has been completely destroyed by the presence of tumour tissue above described (fig. 5). But in the greater portion of the middle whorl and the basal whorl there is no tumour tissue in the portion of the modiolus which is occupied normally by the ganglion spirale. In this region the nerve-cells of the ganglion have entirely disappeared and nothing is left to indicate that they ever existed except the large spaces which they occupied. There is no new-formed connective tissue such as is

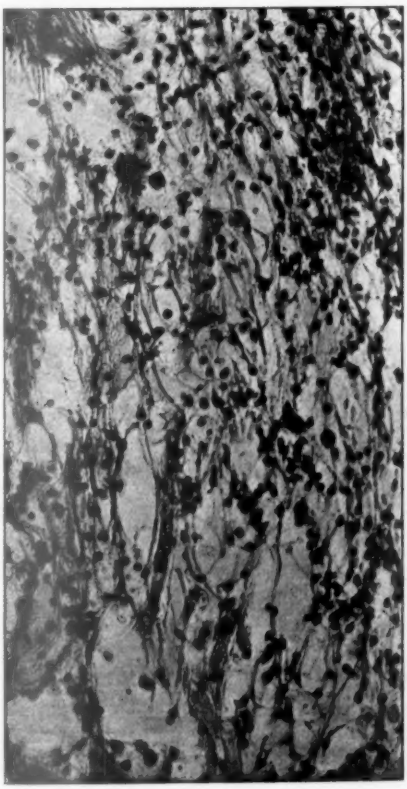


FIG. 10.—Right ear. Ganglion spirale. The nerve cells have all disappeared, but the spaces they formerly occupied are seen. (Zeiss 8 mm. obj. No. 1 eyepiece.)

found as the result of chronic inflammatory activity. The nerve-cells simply seem to have disappeared in the same manner as the organ of Corti in the lowest portion of the basal whorl, as described above. A number of small round cells are present but these show no signs of developing into fibrous tissue. They are particularly numerous in the regions of the blood-vessels.

Left ear. Macroscopic appearances.—In the middle ear of the left side a spherical tumour is found, smooth on the surface and white in colour. The tumour measures about 3 mm. in diameter and it is of hard consistency. It lies on the

inner wall of the tympanic cavity below the stapes. It is pedunculated, and the pedicle can be traced inwards passing through the round window to the inner ear. Except by its pedicle, just described, it is not adherent to any of the surrounding structures (fig. 11).

The posterior surface of the petrous portion of the temporal bone is to a large extent destroyed by the tumour the external limit of which is in close proximity to the posterior crus of the superior semicircular canal (fig. 12).

Internally the tumour extends to the inner extremity of the petrous portion of the temporal bone and even into the adjacent portion of the occipital bone.

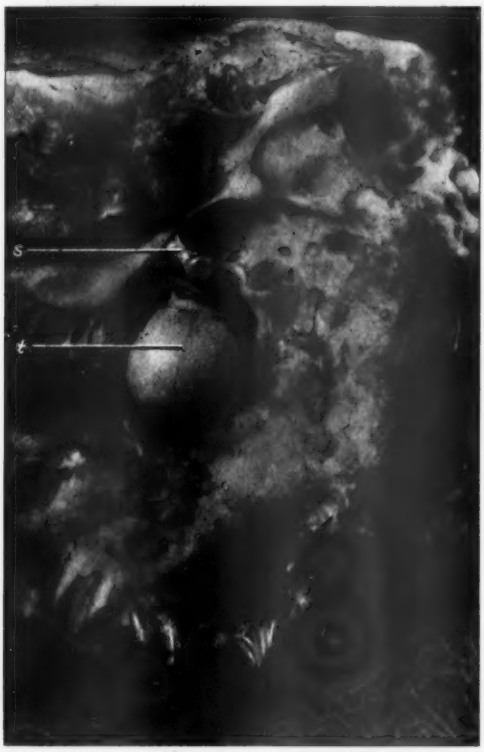


FIG 11.—Left ear. *s*, stapes; *t*, tumour grown out through the round window. (× 4.)

Anteriorly it extends up to the basal whorl of the cochlea (figs. 12 and 13) and to the carotid artery against the wall of which it lies (fig. 13). The growth has extended into the vestibule which it completely fills and also projects for a short distance into the semicircular canals. The bony walls of the internal auditory meatus are completely destroyed.

The middle and basal whorls of the cochlea are filled by the tumour and there is a further extension of the growth through the round window into the middle ear, where it forms the spherical tumour described above (fig. 11). This portion of the

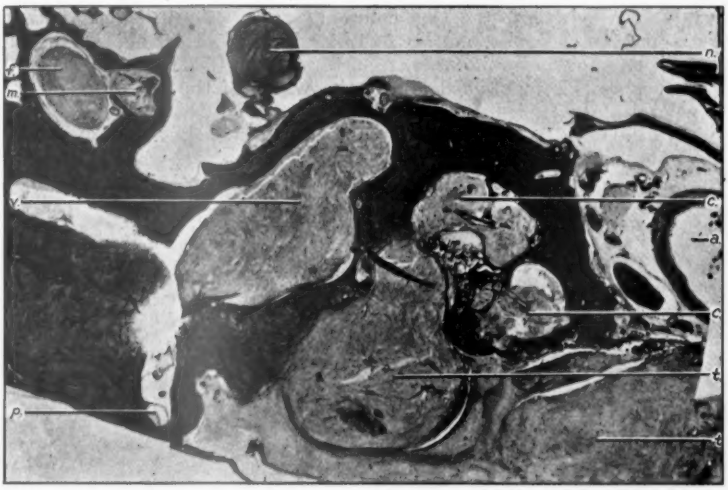


FIG. 12.—Left ear. *f*, facial nerve; *m*, stapedius muscle; *v*, vestibule filled with tumour tissue; *p*, posterior canal; *n*, tumour tissue in middle ear; *c.c*, cochlea filled with tumour tissue; *a*, carotid artery; *t.t*, tumour tissue main growth. (× 4.)

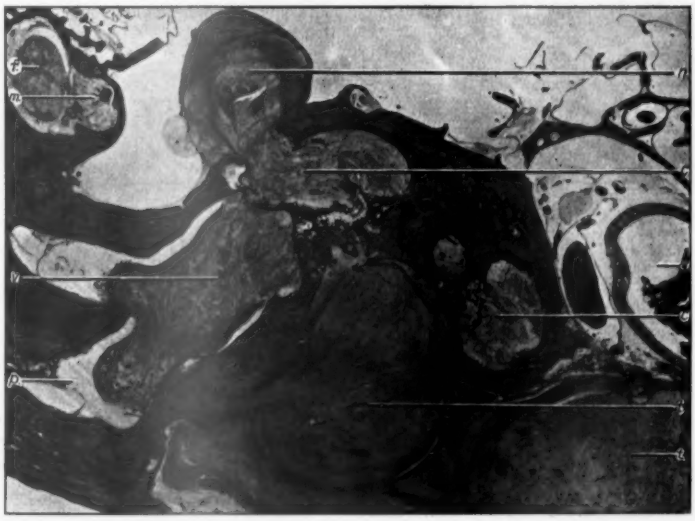


FIG. 13.—Left ear. *f*, facial nerve; *m*, stapedius muscle; *v*, vestibule filled with tumour tissue; *p*, posterior canal; *n*, tumour tissue grown through the round window into middle ear; *c.c*, tumour tissue in cochlea; *a*, carotid artery; *t.t*, tumour tissue main growth. (× 4.)

tumour is seen in microscopic section in figs. 12 and 13. In the vestibule the growth fills the whole cavity and lies externally against the footplate of the stapes. There is no erosion of the bone of the footplate but the latter is dislocated outwards at its anterior extremity by the pressure of the growth (fig. 14).

In the cochlea, as mentioned above, the whole of the basal and most of the middle whorls are occupied by tumour tissue which has entirely destroyed the organ of Corti and all the nerve structures (figs. 12 and 15). A small portion of the bony tissue of the modiolus, however, remains in the middle whorl (fig. 15). In the upper part of the middle whorl and in the apical whorl there is no deposit of tumour tissue. In this latter region there is found a deposit of new-formed bone (fig. 15). It is of interest to observe that this deposit of new-formed bone does not

FIG. 14.

FIG. 15.

FIG. 14.—Left ear: *a*, articular surface of footplate of stapes displaced outwards; *f*, footplate of stapes; *t*, tumour tissue in cochlear; *v*, tumour tissue filling vestibule. (× 20.)

FIG. 15.—Left ear: *b*, bony capsule of labyrinth; *t.t.t*, tumour tissue of middle whorl; *n*, new-formed bone in upper portion of middle whorl and apical whorl; *m*, osseous spiral lamina. (× 15.)

appear to have any direct connection with the bony capsule of the labyrinth, or to be an extension inwards from that structure. There is a sharp line of demarcation between the bony capsule of the cochlea and the new-formed bone in the cochlear canal; and this line of demarcation indicates the position of the endosteum of the capsule of the labyrinth (figs. 15 & 16). Furthermore, the texture of the new-formed bone differs from that of the bony capsule in that it contains a considerable number of spaces which are filled by bone-marrow (fig. 16). The new-formed bone stains more deeply than the adjacent normal bone of the labyrinthine capsule. Indeed it is remarkably similar to that which is found in otosclerosis. In the latter disease, however, the bone is very rarely, if ever, found present in the cavities of the cochlea.

As regards the histological character of the tumour, it appears to consist solely of

FIG. 16.—Left ear: *b*, bony capsule of labyrinth; *c.c.c*, island of cartilage; *e*, line of endosteum of upper part of middle whorl of cochlea; *n.n*, new-formed bone in upper middle whorl of cochlea; *m.m*, marrow spaces in new-formed bone. (× 100.)

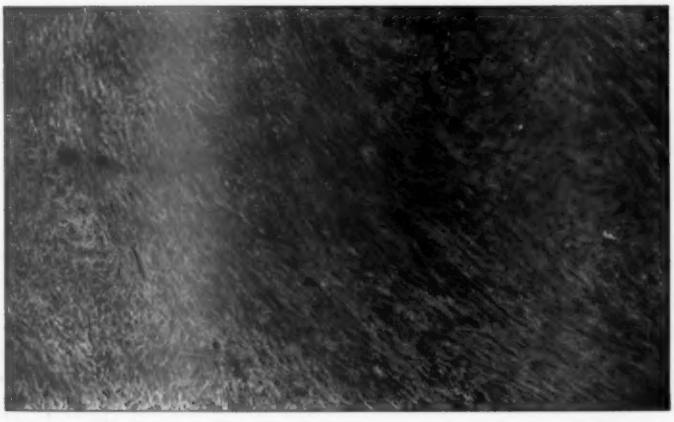


FIG. 17.—Left ear. Section of tumour consisting of fibrous tissue throughout. (× 100.)

fibrous tissue throughout (fig. 17). The cells are of the usual spindle-shape, and the texture of the growth is strikingly homogeneous in all its parts.

This case is interesting from two points of view. First, the features in which it differs from any previously recorded; and second, the way in which it conforms to the usual pathological changes found in cases of acusticus tumour.

As regards the first, the case is unique in three respects. We can find no record of any case in which the tumour has penetrated through the labyrinth and appeared in the middle ear, as was found on the left side in this case. It is interesting to note that many cases have been recorded in which the vestibule and the cochlea were to a large extent filled with tumour tissue, but except in this case the growth remained limited externally to those cavities. The penetration into the middle ear occurred entirely through the round window, although the vestibule was quite as completely filled with the tumour tissue as the cochlea, and the footplate of the stapes was to a certain extent displaced outwards by the pressure of the growth.

Another unique feature of the case is the deposit of newly-formed bone in the cochlear cavities in the apical portion in the left ear. It is to be observed that the area of new-formed bone is not in direct contact with the tumour tissue; and is therefore not a product of response to a direct mechanical irritation. Furthermore, there is no sign of inflammatory activity either in the new-formed bone itself or in the neighbourhood; and it cannot be looked upon as the product of chronic irritation. It takes hæmatoxylin stains more deeply than the adjacent normal bone of the labyrinthine capsule. It is more porous in texture than the latter and the spaces contain marrow. In other words—it is remarkably similar to the new-formed bone which is characteristic of otosclerosis.

It appears to the writer that the most probable explanation of the occurrence of the new-formed bone both in this case and in cases of otosclerosis, is that it is one of the trophic results of disturbance of the nerve supply of the labyrinth as a whole. For it must be remembered that this organ, in common with every other tissue of the body, is under the control of the nervous system so far as nutrition is concerned. We do not know from actual demonstration that the nerve fibres which control the nutrition of the various tissues of which the labyrinth is composed are to be found in the auditory nerve, but it is highly probable that such is the case, and the destruction or degeneration of these fibres may well be the cause of an erratic growth of the tissues which in normal circumstances would not occur.[1]

In this case there is yet another feature which does not seem to have been previously recorded. That is the pathological change which has taken place in the stria vascularis in the right ear. This change has been described above, and reference has been made to the very similar change which is sometimes found in the cochlea of deaf-mutes.

Having described the features which distinguish this case from those hitherto recorded, it remains to refer shortly to that aspect in which it bears a resemblance to other cases of acusticus tumour.

The bilateral symmetry of the case is interesting, and might be expected to be unusual. As a matter of actual fact, however, when neurofibromatosis (von Recklinghausen's disease) affects the auditory nerve, it is by no means unusual to find a tumour on each side. Of course, when a tumour of the auditory nerve occurs independently of neuro-fibromatosis it is almost invariably unilateral.

The effect of the tumour upon the spiral ganglion of the cochlea is very interesting. Wittmaack[2] demonstrated the results of section of the auditory nerve in cats; and showed that, while the vestibular ganglion behaved in the same way as a posterior root ganglion and remained unaffected, the spiral ganglion of the cochlea underwent complete and permanent degeneration. In this respect, therefore, the

1 cf., Gray "Otosclerosis," p. 154. London, 1917.
2 Wittmaack, *Arch. f. Ohr., Nas., u. Kehlkopfheilk.*

spiral ganglion is an exception to Waller's law. The present case confirms Wittmaack's experimental demonstration. The nerve-cells in the ganglion spirals have completely disappeared, as may be seen in fig. 10. It should be added that several other observers have recorded the same phenomenon in these cases (Steurer, Zange, and Lange).

In cases of acusticus tumour, the organ of Corti may be affected or may remain normal in appearance. Panse, Alexander, and other investigators have recorded cases exemplifying both types. The case described in this paper is peculiar in that it shows complete disappearance of the organ of Corti in the basal whorl, whereas that structure appears normal in the middle and apical whorls. Or, at least, if any changes have occurred in these regions they are masked by the post-mortem disintegration which is always found in the human subject when the temporal bone cannot be put into the fixing fluid until some considerable time after death. On the other hand, this disappearance of the organ of Corti in the basal whorl is undoubtedly a pathological change which could not be mistaken for post-mortem maceration.

The literature on the subject is considerable. A long list of references may be found in Cushing's classical work which was published in 1917. A more recent list is given in Lubarsch's "Allgemeine Pathologischen Ergebnisse." In the latter, however, the list is confined almost entirely to German investigators. More recently a particularly interesting paper by Nylen has appeared in the *Acta Otolaryngologica*, 1931.

Discussion.—Dr. A. DE KLEJN: It must be remembered that in the condition described the whole central nervous system may be involved in the tumour formation. In another case of von Recklinghausen's disease the patient came into the neurological clinic deaf and blind, and with symptoms due to lesion in the medulla oblongata. An X-ray examination of the skull was made, and showed no typical disturbances. In that case no skiagrams were taken of the petrous bone. At the post-mortem examination two large acoustic tumours were found. In all cases of central nerve deafness skiagrams should be taken, not only of the whole skull, but also—and especially—of the petrous bone.

Dr. ALBERT A. GRAY: An interesting point is the extension of the growth into the middle ear; this has not been recorded before. The case also confirms Wittmaack's experiment on the degeneration of the cochlear nerve with loss of ganglion cells. When acusticus tumour occurs as part of von Recklinghausen's disease, the tumours are relatively frequently bilateral. Apart from Recklinghausen's disease the tumour is practically never bilateral.

Another interesting feature is the curious deposit of bone in the upper whorl of the cochlea. It looks very much like the new-formed bone of otosclerosis.

The PRESIDENT said that, with regard to the bilateral tumours in Recklinghausen's disease, in Henschen's statistics he recorded 245 unilateral tumours, 24 bilateral; Harvey Cushing, however, had remarked that bilateral tumours were more likely to be recorded than unilateral ones, and the proportion that authority gave was about 1 in 100.

He asked whether there was any difference in the involvement of the temporal bone in the bilateral as opposed to the unilateral cases, because in an advanced case it would be impossible to remove the tumour surgically, unless the whole petrous bone was included in the operation. In some cases Cushing apparently carried out an intracapsular enucleation, making no attempt to remove the whole of the tumour. A second operation might be necessary.

Sir CHARLES BALLANCE said that the first case of auditory nerve tumour that he had seen was in 1887, under the care of Dr. Seymour Sharkey, in the wards of St. Thomas's Hospital, where he, the speaker, had then been for two years aural surgeon.

The patient was a man aged 42, whom he, Sir Charles, was asked to see on account of headache and optic neuritis. The optic neuritis was bilateral, and the patient had been suffering for over a year from tinnitus and slight deafness. He also had attacks of giddiness, and some loss of hearing on the left side. He, Sir Charles, had diagnosed the case as one of tumour of the auditory nerve, but his diagnosis had been ridiculed. The headache and optic neuritis increased and there was partial loss of vision. The patient also had vomiting and

other symptoms and died about six months after admission to hospital. An autopsy was performed and the brain was removed. The late Professor Shattock made a beautiful drawing of the tumour, published in the *Transactions* of the Pathological Society. Since that time he, Sir Charles, had seen a considerable number of such cases, in all of which the tumour had been one-sided. The President's remark that tumours occurred on both sides in only 1 in 100 cases was probably correct; but there was no reason why they should not occur on both sides in Recklinghausen's disease.

A unilateral tumour in an early stage could be easily and successfully removed by free exposure and by the use of the Bovey-Cushing instrument which cut the tissues without burning them, coagulated them and prevented hæmorrhage.

Mr. SYDNEY SCOTT reminded Dr. Gray of a section of the labyrinth which he, the speaker, had shown at a previous meeting which bore out Dr. Gray's findings, an auditory nerve tumour having invaded the labyrinth.

Mr. SOMERVILLE HASTINGS said that the organ of Corti was destroyed in the lower coils of the cochlea rather than the upper coils, and asked whether that was usual in cases of pressure on, or destruction of, the auditory nerve. Had Wittmaack recorded this as the result of his experiments?

Dr. GRAY (in reply) said that in consequence of the erosion of the temporal bone it would have been impossible to get the tumour away completely. It was not Wittmaack who discovered the degeneration of the organ of Corti in acusticus tumour cases, but Panse. In some cases the organ of Corti underwent complete degeneration throughout the cochlea, and in others it remained undamaged. But, as Mr. Somerville Hastings pointed out, the curious feature about this case was that the organ of Corti disappeared in the lowest wall, not the upper. If the patient had lived longer the upper part also might have disappeared.

Pathological Changes in the Auditory Nerve in Otosclerosis and their Significance Clinically, especially with regard to Paracusis Willisii.

ALBERT A. GRAY, M.D.

In the writer's work on "Otosclerosis" published 15 years ago[1] the pathological changes which were found in the four cases of the disease are described. Towards the end of the description of each case there is a statement to the effect that, although no pathological changes were demonstratable in the cochlear nerve, it must not be concluded that such changes did not exist. They might quite probably be present, but if so, the methods of microtomy and microscopy then available were not sufficiently delicate to show them.

In the intervening 15 years, improvements in the technique of examining the organ of hearing have been made by the present writer and others. By means of these improvements it is now possible to detect pathological changes which were not visible before, and by their application the writer has now been able to demonstrate pathological changes in the cochlear nerve in cases of otosclerosis.

In the following pages these changes will be described, and their significance in respect of our views on paracusis willisii in particular and otosclerosis in general, will be considered.

Over a long period of time the writer has had the opportunity of obtaining the auditory nerves from several subjects who had suffered from otosclerosis during their life. In some cases the temporal bones were also obtained. These have been prepared and mounted as microscopical sections, and in this paper some of the results of the examination of these will be given, chiefly with regard to the condition of the cochlear nerve.

1 Gray: "Otosclerosis: Idiopathic Degenerative Deafness." London, 1917.

In all cases formalin was the fixing agent employed, sometimes in combination with alcohol and sometimes with normal saline. The staining in all cases was done with iron alum and hæmatoxylin. The embedding of the preparations was done either in paraffin or celloidin or both together; and, since the lipoid substances which are present in the medullary sheath are dissolved away in these methods of embedding, no reference can be made to the changes which may occur in them in otosclerosis. For their investigation special methods are required.

Case I.—The cochlear nerve was obtained from a case of otosclerosis in which the deafness had existed for three years. That is to say, it was a comparatively early case.

The clinical report, as well as the pathological changes found in the bone, are recorded in the writer's "Otosclerosis,"[1] and will only be referred to here in so far as they have a direct bearing on the matter in hand.

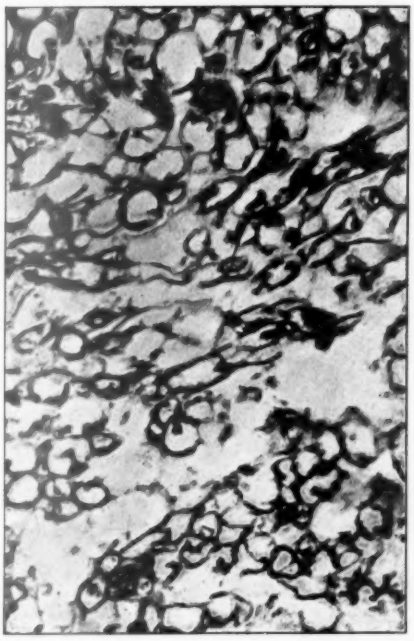


FIG. 1.—Cochlear nerve in early stage of otosclerosis. *Case I.*—Transverse section. Upper part of field shows absence of spiral filament in many fibres, but the neurilemma is well preserved and axis-cylinder present. It will be observed that when the spiral filament has gone the axis-cylinder lies at the side of the fibre against the neurilemma. The lower part of the field shows the neurilemma in process of degeneration and large spaces forming. (Zeiss 8 mm. obj. No. 8 eyepiece.)

In fig. 1, which shows a transverse section of the cochlear nerve, it will be seen, in the *upper* portion of the photograph, that in a large number of the fibres the spiral filament is not present; indeed this structure is only found in a few. In a very considerable proportion of the fibres the axis-cylinder is still present, but it is interesting to observe that in most, if not in all, of those fibres in which the medullary sheath is absent, the axis-cylinder is found not in the middle of the fibre, which is its normal position in a healthy nerve, but at the side, and lying in contact with the neurilemma. The neurilemma itself, although by no means normal in appearance, is fairly complete in most of the fibres, which are to be seen

[1] Gray, op. cit., p. 74.

in the upper portion of the photograph. In the *lower* portion of the photograph it is obvious that the pathological changes are more advanced than in the upper. The medullary sheath is found in very few of the fibres, and the axis-cylinders are relatively few in number. The neurilemma in this portion of the photograph is seen to be undergoing marked degeneration. It has, to a large extent, disappeared altogether from many of the fibres, with the result that large spaces are formed by the coalescence of several adjacent ones. In a few fibres, however, it still appears to be fairly normal in appearance.

In fig. 2 is shown a photomicrograph of a longitudinal section, which shows the pathological changes rather better than a transverse one. The spiral filament is seen to be absent altogether from some parts of a fibre, but present, though in a rather broken-down

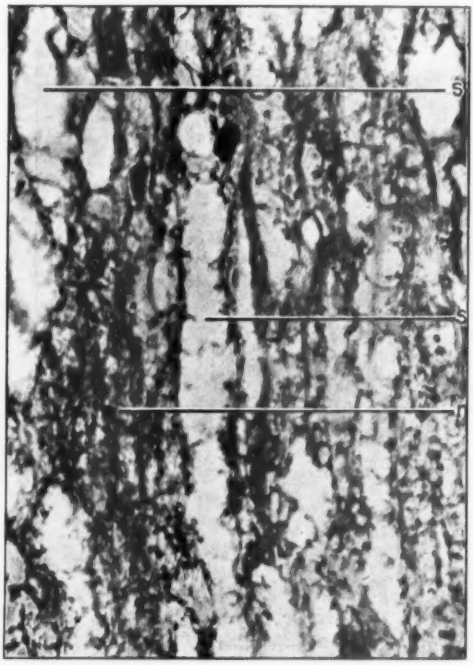


FIG. 2.—Cochlear nerve in early stage of otosclerosis. *Case I.*—Longitudinal section. *n*, Fibres with axis cylinder spiral filament and neurilemma still normal; *s s*, large spaces formed by the coalescence of several fibres resulting from the breaking down and disappearance of the medullary sheath and neurilemma. (Zeiss 8 mm. obj. No. 4 eyepiece.)

condition, in other parts. Furthermore, the comparatively sharp outline of a healthy nerve-fibre is noticeably absent in many of the fibres in this case. This is owing to the disappearance of the neurilemma or, in some parts, to the fact that the latter, though still present, stains very faintly owing to its degenerated condition.

This case is interesting in respect of the bearing it has upon the relationship of the bony change in the capsule of the labyrinth to the changes in the auditory nerve. Almost all otologists recognize that the symptoms of the disease in its later stages indicate a diseased condition of the nerve, but very many assume that the changes in the nerve are secondary, and due to the interference with the relief to pressure changes within the labyrinth, resulting from bony fixation of the stapes. Now in this case, although bony changes of the typical otosclerotic type were present in

the usual place in front of the oval window in both ears, these changes have not affected the stapedio-vestibular articulation on either side, and therefore could not interfere with changes in pressure in the labyrinthine fluids.

A further interest centres in this case in that it reveals the fact that the changes in the nerve are found in an early stage of the disease, and not, as is frequently assumed, exclusively in the later stages.

Case II.—There is no clinical report of this case. All that could be ascertained was that during her life the patient was dull of hearing, but could hear conversation quite well if the voice were raised a little.

The stapes was fixed in the oval window in both ears by bony ankylosis. A transverse section of the cochlear nerve is shown in fig. 3.

In a considerable portion of the field the nerve fibres showing definite pathological changes are comparatively few in number and in this portion the neurilemma in particular is well stained and shows little signs of degeneration. In the remaining portion of the field, there is very definite evidence of degenerative processes in the nerve fibres. In most of them the medullary sheath has disappeared and the neurilemma stains faintly and in many of the

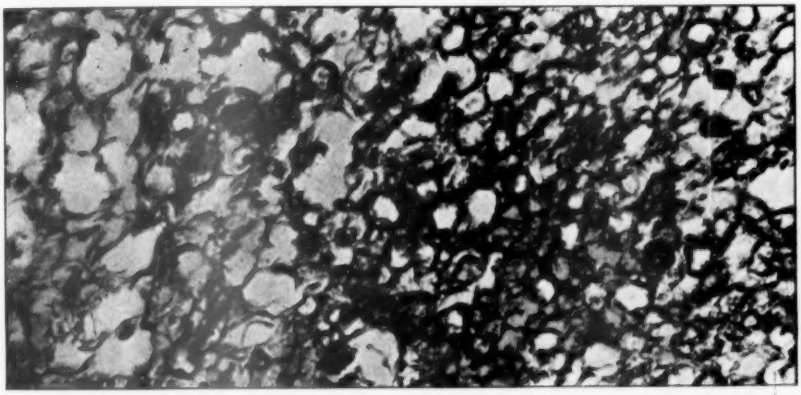


FIG. 3.—Cochlear nerve in early stage of otosclerosis. *Case II.*—The position of the field to the right shows almost normal conditions of nerve fibres. The left portion shows disappearance of the spiral filament and some degree of degeneration of the neurilemma. Transverse section. (Zeiss 8 mm. obj. No. 4 eyepiece.)

fibres portions of it are lost altogether, with the result that adjacent fibres can be seen in the process of coalescence, thus producing comparatively large empty spaces.

The axis-cylinders are still present in some of the spaces and can be seen lying in contact with the neurilemma. In a few of the spaces, however, they seem to have disappeared altogether.

There is no sign of any inflammatory condition, past or present. There is no round cell infiltration nor any new-formed connective tissue. The changes are purely degenerative in character.

Case III.—In this case also there is no clinical history, but it was ascertained that during life the patient was very deaf, but could hear the loud voice when spoken close to his ear. His wife could not remember whether he had ever heard better in a noise or not. The stapes was fixed by bony ankylosis in both ears.

Fig. 4 shows a transverse section of the cochlear nerve. It will be seen that in the whole field there are few nerve-fibres that present a normal appearance.

The great majority show appearances similar to those found in the more seriously affected portions in the two cases previously described. In by far the greater number of fibres the spiral filament has disappeared, and in a great many the neurilemma stains faintly in some parts and in other parts has disappeared altogether.

The axis-cylinders are present in very considerable numbers and are to be seen in fibres which have lost their spiral filament and even in some of those in which the neurilemma is degenerated and in some portions lost altogether.

In those fibres in which the spiral filament is lost, it will be noticed that the axis-cylinder usually lies close up against the neurilemma, if the latter is still present in that fibre. There is no sign of inflammatory changes, past or present.

It is to be noticed, however, that there are still a few healthy nerve-fibres with the spiral filament still present and the neurilemma intact.

Case IV.—No clinical report was obtained in this case, but from the nursing attendants it was ascertained that the patient was extremely deaf. They could, however, make him hear and understand conversation by shouting loudly very close to his ear. Whether he had ever been the subject of paracusis is not known.

The stapes is fixed by new-formed bone in the oval window in both ears and was, except for the outer portions of the crura, embedded in bone.

The pathological changes in the cochlear nerve were much more pronounced than in any of the three cases previously described. The nature of the changes was, however, very similar.

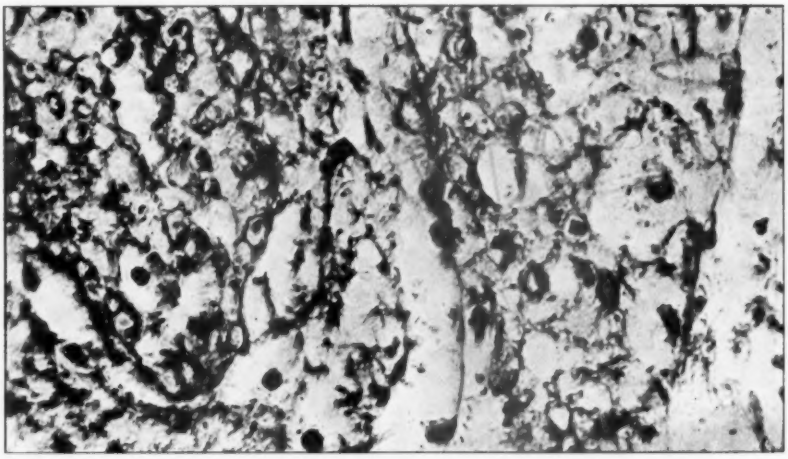


FIG. 4.—*Case III.*—Very considerable degeneration of the nerve fibres is shown, especially to the right and below. (Zeiss 8 mm. obj. No. 4 eyepiece.)

Fig. 5 shows the cochlear nerve on transverse section.

The major portion of the field consists of large spaces formed by the coalescence of several adjacent nerve-fibres by the breaking down of the neurilemma which separated them.

The spiral filament has disappeared in almost all the fibres, though here and there a few can be found in which no sign of disease is present.

The neurilemma is very seriously damaged, and stains very faintly except in a few scattered patches. The axis-cylinders are relatively much fewer in number than in the three previous cases, but even in this advanced case of deafness they are not destroyed to the same extent as is the spiral filament or even the neurilemma, as was observed in the other cases.

Fig. 6 shows a longitudinal section of the cochlear nerve which reveals the same features as those just described, but viewed from a different aspect. The process by which the large spaces are formed by the breaking down of the neurilemma is very clearly shown in this figure.

There is no sign of inflammatory activity, nor is any new-formed fibrous tissue present. The process is a purely degenerative one.

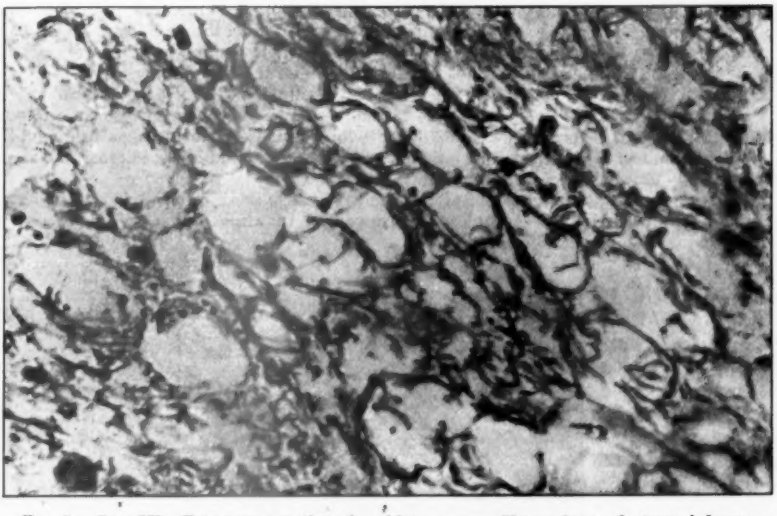


FIG. 5.—*Case IV.*—Transverse section of cochlear nerve. Very advanced stage of degeneration. The spaces formed by breaking down of the neurilemma are very large, and what is left of the neurilemma stains faintly. Axis-cylinders comparatively few in number. (Zeiss 8 mm. obj. No. 12 eyepiece.)

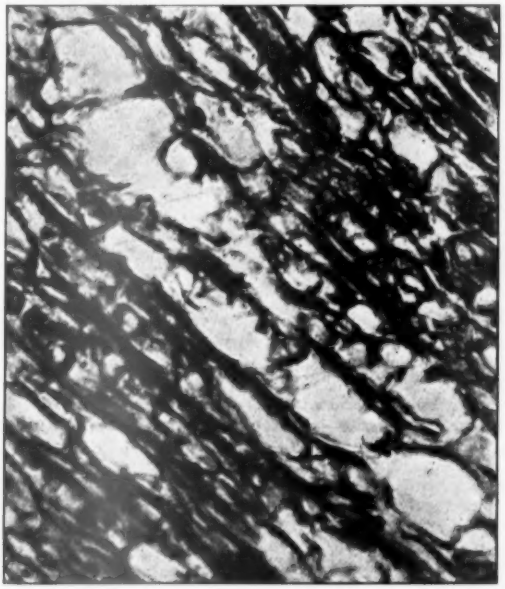


FIG. 6. *Case IV.*—Longitudinal section of cochlear nerve. Hardly a trace of the spiral filament is found. Large spaces are seen, formed by breaking down of the neurilemma. (Zeiss 8 mm. obj. No. 12 eyepiece.)

Case V.—This case is not one of ostosclerosis, but of pure senile deafness. The patient died at the age of 101 years, and for many years before her death she had been so deaf that no one could make her hear at all. The writer saw her a few months before she died, and the sound of a loud dinner bell was not heard even when rung close to her head.

A photomicrograph of a section of her temporal bone is shown in the writer's "Atlas of Otology," and it will be seen that there is no bony change in the capsule of the labyrinth, and that the stapes lies freely movable in the oval window. The changes in the cochlear nerve are shown for the purpose of comparison with those found in otosclerosis, as recorded in the previous four cases.

Fig. 7 shows a transverse section of the cochlear nerve in this case. It will be observed that the spiral filament has completely disappeared in almost every fibre, though little fragments of it may be seen here and there.

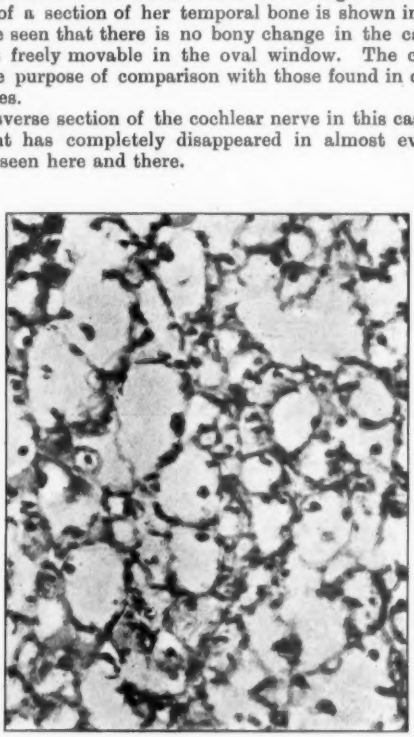


FIG. 7. *Case V.*—Senile deafness. Very little trace of spiral filament is seen, and large spaces are formed by the disappearance of the neurilemma. Axis-cylinders however are numerous. Transverse section. (Zeiss 8 mm. obj. No. 8 eyepiece.)

The neurilemma also has undergone considerable degeneration, and there are many empty spaces formed by the coalescence of several adjacent fibres.

But this change is hardly any more pronounced than in Case No. 4 of otosclerosis just recorded. The most striking feature is the remarkable extent to which the axis-cylinders are apparently unaffected. Over the whole field axis-cylinders are present in large numbers, and in this respect senile deafness stands out in striking contrast with advanced cases of otosclerosis.

The facts concerning the pathological changes found in the four cases of ostosclerosis described above may be summarized as follows:—

In the early stage of the disease, the medullary sheath appears to be the first to undergo degeneration, as shown by the breaking up and loss of the spiral neurokeratin filament. The next change is the breaking down of the neurilemma with the resulting formation of large spaces formed by the coalescence of several adjacent nerve-fibres.

Finally there is a tendency towards the disappearance of the axis-cylinder, though even in very advanced cases some are still present.

The most striking difference, so far as changes in the cochlear nerve are concerned, between otosclerosis and senile deafness, is the persistence with which the axis-cylinder survives in senile deafness. Of course it is highly probable that, in a case of such profound senile deafness as that just recorded, other and more serious changes would be present, either at the synapses of the neurons or in the projections of the auditory nerve in the central nervous system.

Before passing on to consider the direct bearing which these changes in the cochlear nerve have upon our conception of otosclerosis, it is desirable to point out certain fallacies commonly held with regard to the cause of the clinical symptoms and the pathological conditions.

Many otologists appear to hold the view that the deafness is due to the fixation of the stapes, although many others admit that the so-called secondary changes in the nerve bring about an increase in the deafness. But Cases 1 and 2 in the writer's work on otosclerosis [1] show clearly that the deafness makes its appearance before the stapes is fixed. In Case 1 the deafness was very considerable in both ears and had been in existence for three years. In Case 2 it had been noticed for only one year, but in spite of its comparatively short duration it was fairly severe in degree, the whispered voice which is normally heard at a distance of 6 to 7 yards, being only heard at a distance of $1\frac{1}{2}$ ft., and the watch, normally heard at $2\frac{1}{2}$ yds, was only heard at a distance of 2 in.

Another erroneous idea commonly held is that the essential feature of the change in the labyrinthine capsule is the deposition of new-formed bone. Now the deposition of new-formed bone is not the crucial feature as regards the bony change. Absorption of bone is the primary and sometimes the only change, as is shown in Case 2 [2]. It is true, however, that in the great majority of cases the deposition of bone does follow the absorption.

The pathological changes in the cochlear nerve which have just been demonstrated must affect very markedly our attitude towards the otosclerosis problem in general and the symptomatology in particular. In the following pages the symptom which will be considered in most detail will be paracusis willisii, but some remarks will be made later in regard to tinnitus and the vasomotor reflex of the tympanic membrane.

At one time the explanation of paracusis most commonly accepted was that the larger vibrations of the loud disturbing sound produced movements of the stapes, which allowed the smaller vibrations caused by the voice to reach the fluids of the labyrinth, which they were not able to do by their own unaided energy. For a number of years, however, I have noticed that an increasing number of otologists refuse to accept this explanation, though none of those of whom I have made inquiries had any explanation to offer as a substitute for that which they had discarded.

In the writer's work on otosclerosis [3] just referred to there are recorded two cases, which alone give almost clear proof that paracusis cannot be explained by fixation of the stapes. In the case recorded on p. 92 in that work, paracusis was strikingly present in spite of the fact that there was no fixation of the stapes in either ear. Indeed, owing to the fact that the bone in the affected region had been absorbed without any subsequent deposition of new bone, the stapes and adjacent regions of the walls of the oval window were more mobile than normal. On the other hand, in the case recorded on p. 104 the stapes was fixed by bony ankylosis in both

[1] Op. cit., pp. 74 and 92.
[2] Op. cit.
[3] Op. cit., pp. 92 and 104.

ears. The patient had suffered from gradually increasing deafness for twenty-five years, and at the time of the clinical otological examination she was very deaf. Yet this patient had never at any time noticed that she heard any better in a noise.

From a consideration of these two cases, it follows that the explanation of the occurrence of paracusis must rest on grounds other than the fixation of the stapes. The writer ventures to suggest that the occurrence of paracusis depends upon the changes in the cochlear nerve described in the earlier portion of this paper.

It is important to point out that the term paracusis willisii may mean either that the patient hears absolutely better in a noise than in silent surroundings, or that, relative to normal hearing individuals, he hears better in a noise, but not absolutely better than he does in a surrounding silence. It is probable that both conditions occur and the explanation of the phenomenon which is given in the following pages applies equally well to both.

Under normal physiological circumstances the axis-cylinder of a nerve fibre is insulated by the medullary sheath, and very probably also to a certain extent by the neurilemma, since some of the fibres of the sympathetic system have no medullary sheath. Nerve impulses, therefore, cannot under healthy circumstances pass from one nerve fibre to the adjacent ones. The strength of the nerve current depends upon the number of impulses per second and not upon the intensity of the individual impulses, since it has been demonstrated by Adrian that nerve impulses are of equal intensity when a nerve fibre is stimulated. The resistance offered to the nerve current is found, for the most part, at the synapse of the neuron. In the case of a sensory nerve, therefore, the intensity of the sensation may be increased either by increasing the number of impulses per second or by diminishing the resistance at the synapses, and conversely. So long as the axis-cylinder is insulated by the medullary sheath and neurilemma, the impulses will not be lost nor be able to pass into the surrounding adjacent nerve fibres, and the strength of the nerve current will be maintained up to the synapse of the neuron.

But if the medullary sheath and neurilemma are damaged and no longer able to insulate the axis-cylinder, then the impulses are able to a certain extent to escape into the surrounding tissues and the strength of the current diminishes as it passes up the nerve fibre to the synapse. But if there happened to be several adjacent nerve fibres in which also the axis-cylinder is not insulated on account of the damaged condition of the medullary sheath and neurilemma, then it is obvious that impulses can pass from one axis-cylinder to adjacent ones and vice versa.

In otosclerosis, as has been demonstrated in the earlier part of this paper, there are found pathological changes such as those just suggested, and we may expect therefore that, under these circumstances, nerve impulses may pass from one nerve fibre to adjacent ones, which would not be possible in a normal healthy cochlear nerve. On this basis it appears to the writer that some of the clinical symptoms of otosclerosis can be explained.

It is necessary, at this point, to make a brief reference to the anatomical arrangement of the fibres of the cochlear nerve. In general, nerve fibres which come from adjacent portions of the organ of Corti remain adjacent to one another in their course through the bony spiral lamina to the ganglion spirale, and, further, nerve fibres from the ganglion spirale passing down into the modiolus also remain adjacent to one another. Thus, fibres from the organ of Corti in the apical region of the cochlea pass in towards the modiolus together and turning downwards they form the central core of the cochlear nerve.

On passing downwards from the apex, the nerve fibres coming inwards are successively laid on outside those which have come from above. Hence, as the cochlear nerve leaves the modiolus to enter the internal auditory meatus the nerve fibres from the apical regions of the cochlea lie in the central portion of the nerve, while those from the basal parts of the cochlea are found in the periphery. As far

as the writer has been able to observe, this arrangement of the fibres remains the same along the course of the cochlear nerve in the meatus, and indeed this is what would be expected.

With these anatomical and physiological facts at hand, and taking them in conjunction with the pathological changes described in the first part of this paper, we are, I think, in a position to give a reasonable explanation of that curious feature paracusis willisii, so often noticed in cases of otosclerosis.

Fig. 8 is a diagram showing in transverse section a portion of the innermost part of the cochlear nerve of a normal hearing individual; that is to say, fibres which come from the apical whorl and the upper part of the middle whorl of the cochlea in which region the lower notes of the scale are transformed into nerve-impulses. Fig. 9 is another diagram representing the same portion of the cochlear nerve in the case of an individual who is the subject of otosclerosis, and in whom, therefore, the axis-cylinders are not completely insulated, as has been demonstrated in the previous pages of this paper. The individual with the normal cochlear nerve may be called "B" and the one who is suffering from otosclerosis "C."

Let it be supposed that a conversation is being carried on between these individuals B—C and another individual who may be termed "A."

We will assume that A is speaking at a given moment and that the three individuals are together in comparatively silent surroundings. Taking a very short period of time, say a fraction of a second, during A's conversation, let us try and visualize what is occurring in the fibres of the cochlear nerve in B and C respectively.

In the case of B, who has a normal nerve, at a given moment of A's conversation certain fibres will be transmitting the currents which are created by A's voice at that moment. These fibres, shown outlined in thick lines in the diagram, being well insulated, will not permit any loss of nerve-impulses, and the current will be transmitted upwards in practically its full strength. But in the case of C a different state of matters is found. The nerve fibres, which are carrying the current which is created by the different tones in A's conversation, are not properly insulated. Consequently nerve-impulses escape from these fibres and pass into the adjacent nerve-fibres at points where the latter have lost their neurilemma and medullary sheath. These impulses, therefore, are lost so far as they would enable C to hear A's conversation. Such is the case when the surroundings of the three individuals are silent.

The conditions are different when the conversation is being carried on in noisy surroundings, as in the roar or rattle of a train or in the loud noise which occurs in many factories, etc. Under these circumstances the nerve fibres which are carrying the currents created by A's conversation are surrounded by fibres which are carrying currents created by the noise of the factory or the roar of the train. Furthermore, since these latter fibres are carrying currents produced by a stronger stimulus, the nerve-impulses will be greater in frequency in them than in the fibres carrying the currents produced by A's conversation.

But if the insulation of the axis-cylinders is imperfect owing to the loss in patches of the medullary sheath and neurilemma, as is the case in the otosclerotic individual C, then the fibres which are carrying the currents created by A's conversation will gain from the adjacent fibres carrying those produced by the surrounding noise more impulses than they will lose.

In the case of the healthy nerve, on the other hand, there can be no passage of impulses from one nerve-fibre to adjacent ones, and the currents created by the surrounding noise in B's case cannot be diverted to strengthen the currents created by A's conversation. To put the matter in as concise a form as possible, it may be expressed thus: In the normal individual the nerve currents in the cochlear nerve created by the conversation derive no increase of intensity from the nerve currents produced by the surrounding noise, whereas in the case of the paracusic

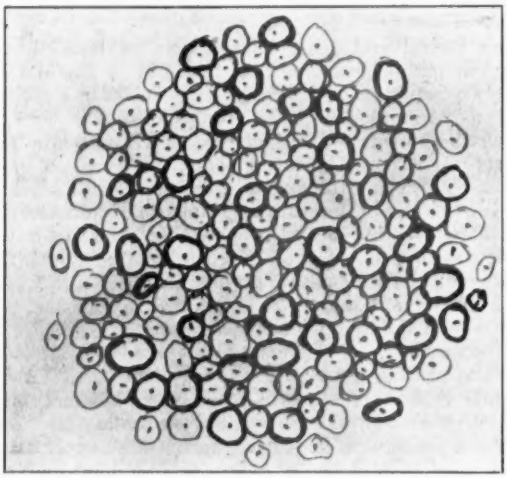


FIG. 8.—B.

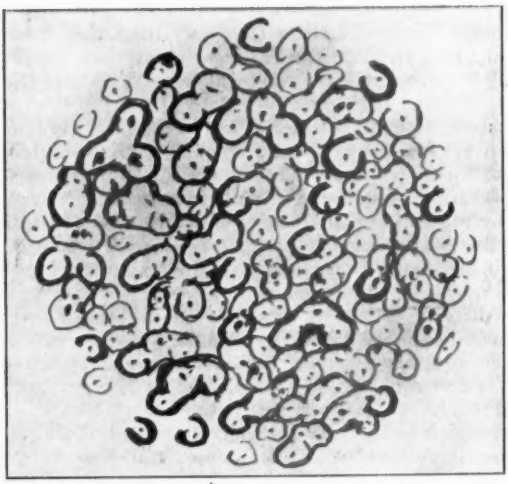


FIG. 9.—C.

individual they do. Consequently, the latter hears relatively better in a noise than a normal individual. Furthermore, it is quite possible that the paracusic may hear absolutely better in a noise than in silent surroundings.

In vol. xliii, p. 261, of the *Journal of Laryngology and Otology*, Mr. Somerville Hastings described a condition which had never previously been observed. He found in a certain number of deaf patients who were the subjects of paracusis that, if a disturbing sound were applied to one ear and a testing sound (a tuning-fork) were at the same time applied to the opposite ear, the testing sound was heard better than when the disturbing sound was not applied to the other ear. The condition was found to exist in several patients and repeated examination proved the unquestionable reality of the facts. At first sight it would appear difficult to find an explanation of this condition of crossed paracusis. But if the writer's hypothesis of ordinary paracusis willisii be applied, then the phenomenon can be accounted for without much difficulty. In the writer's explanation of the occurrence of ordinary paracusis given in the preceding pages the cochlear nerve was considered as being diseased only in its course from the medulla to its distribution in the cochlea. But there is no reason why similar pathological changes should not occur in the intracerebral projections of the nerve. Now, the cochlear nerve on its passage through the medulla and up to the higher centres of the brain, undergoes a partial decussation similar to that which occurs in the optic nerve at its commissure. That is to say, some of the fibres of the cochlear nerve pass up to the higher centres of the same side, while others cross over and pass up to the corresponding centres of the opposite side. Hence, after the decussation has taken place, fibres from the left ear will pass along adjacent to corresponding fibres from the right ear up towards the higher centres. Therefore, a lesion in this region will affect fibres coming from both right and left ears; and, if the lesion should be of the same nature as that which has been demonstrated in the early pages of this paper as affecting the cochlear fibres between the medulla and the cochlea itself, then the same phenomena may occur. That is to say, nerve impulses will be able to pass from one nerve fibre to adjacent nerve fibres. When, therefore, the disturbing noise is applied to say, the right ear, nerve impulses in the fibres in this region above the decussation can pass over to adjacent fibres coming from corresponding regions of the cochlea of the left side. The nerve-current aroused by the testing sound in the left ear will thus gain in strength by the impulses which it receives from the right ear, because the noise in the right ear will produce a stronger nerve-current, since it is louder and causes a greater stimulation of the peripheral sensory end-organs. In fact, in these cases of crossed paracusis precisely the same phenomenon is taking place as that occurring in the stem of the auditory nerve between the medulla and the cochlea, and consequently the testing sound applied to the left ear will be heard louder than it is when there is no disturbing sound applied to the right ear.

Paracusis is a symptom which, though it may endure for many years in the course of a case of otosclerosis, does tend ultimately to disappear, and, in view of the explanation of its occurrence just given, there is not much difficulty in understanding why it should disappear. As the disease progresses and as age advances, the axis-cylinder itself undergoes retrograde changes, either in its course or in the region of the synapse, and becomes unable to transmit the nerve-current as it does when in a healthy condition.

Tinnitus is another of the common symptoms of otosclerosis for which no explanation in the least degree satisfactory has ever been given, so far as the present writer is aware. He, therefore, offers the following explanation which may perhaps be worthy of consideration.

The axis-cylinder of a nerve fibre in a healthy condition is remarkably well protected by the neurilemma and medullary sheath against the products of metabolism in the surrounding tissues, which from their chemical constitution

might have a damaging effect and, by irritating it, produce symptoms corresponding to the particular function which that nerve fibre subserves. Thus, the axis-cylinder of a nerve fibre of common sensation, exposed under these conditions, might give rise to a subjective sensation of pain, those of the eye to subjective sensations of light and those of the olfactory nerve to parosmia.

Now, as has been shown above, the axis-cylinders of many of the fibres of the cochlear nerve in a case of otosclerosis have to a large extent lost their protective covering and are exposed to the injurious products of metabolism in the surrounding tissues. Under these circumstances, therefore, it would not be surprising if subjective sensations of a sound should be perceived by the patient. This explanation would account for one curious feature in regard to tinnitus and that is the fact that in a certain proportion of cases it is the first sign of disease. In the majority of cases it is true that deafness is the first symptom, but the fact remains that in a considerable percentage the deafness is preceded by tinnitus.

The facts demonstrated and the suggestions made in the preceding pages have very obviously an important bearing upon the otosclerosis problem in general. In his work on otosclerosis the present writer made the suggestion that when the clinical and pathological facts are considered together the most natural conclusion at which we may arrive is that the disease is a degenerative process affecting the organ of hearing as a whole, and not a mere local change in the bony capsule of the labyrinth. The facts concerning the changes in the fibres of the cochlear nerve described above lend support to this view.

It has been shown that these changes in the nerve fibres may occur before ankylosis at the stapedio-vestibular articulation has taken place, and they cannot, therefore, be looked upon as secondary changes resulting from interference with the pressure changes within the labyrinth.

As otologists, we have allowed these changes in the bony capsule of the labyrinth to influence our judgment far too much, both from the clinical and the pathological points of view. It is difficult to see, for example, how a change in bone in a very minute portion of the labyrinthine capsule could produce the greatly diminished sensitiveness of the tympanic membrane and the sluggish vasomotor response of the blood-vessels of that membrane which is so strikingly characteristic of otosclerosis.

But, having escaped from the bondage of the osseous change in the capsule of the labyrinth, we must be careful not to fall too much under the spell of the pathological changes in the cochlear nerve which have been described in this paper. These changes are no doubt responsible for some of the worst symptoms of the disease, and from that point of view are much more important than the osseous changes in the labyrinthine capsule. But they do not by themselves explain all the phenomena characteristic of the disease. They do not, for example, explain the occurrence of the bony change referred to, nor do they explain the diminished sensitiveness and sluggish vasomotor response of the tympanic membrane or the diminution in the secretion of the wax.

The pathological changes in the bone and the auditory nerve must be looked upon as characteristic of the disease and also as the causes of the symptoms, but it is impossible to look upon either of them as the cause of the disease itself. This must be sought for elsewhere, and it will be the business of otological research to continue the quest and endeavour to ascertain what change in the body is capable of producing these changes in the bone of the labyrinthine capsule and in the auditory nerve. And if the writer may be allowed to speculate for a moment, he would suggest that this mysterious change is to be looked for in the nerve structures associated with the sympathetic nervous system. It must be remembered that the nutrition of every organ and tissue in the body is under the control of this autonomous system. Whenever an organ or a structure functions, a reflex is started in that organ or structure and passes by various paths, according to the structure in

question, to the sympathetic system, and from there effects an alteration in the calibre of the blood-vessels supplying the structure and so maintains it in a healthy state of nutrition. And the organ of hearing is no exception to this rule in any of its parts. If the reflex continually fails to act any or all of the tissues of which the organ of hearing is composed will undergo degenerative changes. The writer's suggestion is that these degenerative changes in the organ of hearing constitute the condition which we call otosclerosis. And in support of this suggestion it may be pointed out that all the changes which are to be found in otosclerosis are degenerative in character and not inflammatory. This is true of the changes in the tympanic membrane, in the bony capsule of the labyrinth and in the auditory nerve. The suggestion is further supported by the fact which is observed clinically in cases of otosclerosis, that the vasomotor response of the tympanic membrane is very sluggish and sometimes absent altogether. It requires indeed no very great stretch of the imagination to suppose that a similar gradual loss of the vasomotor reflex occurs in the blood-vessels supplying the bony capsule of the labyrinth and the fibres of the auditory nerve.

If I may be allowed to digress into an allied branch of medicine, I would like to suggest that an explanation of atrophic rhinitis may be given similar to that just given for otosclerosis. The two diseases present many parallelisms. They are both essentially diseases of a special sense and in both there is a slowly progressing loss of that sense. Both are frequently accompanied by subjective sensations characteristic of that sense, tinnitus in the one case and parosmia in the other. Both are accompanied by a diminished sensitiveness of the superficial tissues and in both the vasomotor reflex, which should occur on mechanical stimulation of those tissues, is either absent or very sluggish. In both there is a diminution in the secretions of the two organs—wax in the case of one and nasal mucus in the case of the other. Both diseases tend to make their appearance most commonly about the same period of life, and hereditary influence is conspicuously present in a large number of cases in both.

Women are rather more liable to both atrophic rhinitis and otosclerosis than are men, and in the days when chlorosis was a very common disease, otosclerosis and atrophic rhinitis frequently made their appearance when young women were affected by that form of anæmia.

It appears to the writer, therefore, to be very probable that a common causative factor is active in these two diseases—otosclerosis and atrophic rhinitis—and that this factor is a defect in the vasomotor reflex arcs by means of which the nutrition of the tissues is maintained—in the organ of hearing in one case, and in the organ of smell in the other.

Summary.

In otosclerosis there is a degeneration of the fibres of the cochlear nerve, which appears first in the medullary sheath and neurilemma, and later in the axis-cylinder.

This process occurs independently of the fixation of the stapes or of the bony change in the capsule of the labyrinth, and it probably precedes both. Deafness occurs as a result of the degeneration of the fibres of the cochlear nerve before the stapes is fixed.

The clinical picture of otosclerosis is produced for the most part by this degeneration of the cochlear nerve, and only to a minor degree by the fixation of the stapes. The latter may add to the deafness already present and may also account for the relatively prolonged bone conduction. Paracusis willisii, tinnitus and for the most part also the deafness, are due to the diseased condition of the nerve.

The diminished secretion of wax in the meatus, the sluggish vasomotor reaction and accompanying diminished sensitiveness of the tympanic membrane, the bony

change in the capsule of the labyrinth and the degeneration of the cochlear nerve are independent of each other and do not stand in the relationship of cause and effect. They are called into existence by some common factor which is probably to be looked for in the vasomotor arc which controls the nutrition of the structures of the organ of hearing as a whole. These changes in the various structures are all degenerative in character and not inflammatory. They may occur in varying degree in the different structures in different individuals. Hence the clinical picture of otosclerosis varies within fairly wide limits in different cases.

Discussion.—Sir JAMES DUNDAS-GRANT suggested that many cases of paracusis might be due, not to the action of the noise on the patient, but to the raising of the voice on the part of the person to whom the deaf person was listening. On one occasion he had had a young woman patient suffering from paracusis and in an advanced stage of otosclerosis, but without adhesions. When he put the noise machine on the patient's head she heard worse but when he put it on her mother's head and she (the mother) began to speak, the girl said "I hear you; you are speaking through a telephone." When the accompanying person and the patient were together, the noise usually of a deep pitch deafened the person with good hearing, while not intensifying the deafness of the patient who was deaf mainly to the deep tones as in otosclerosis. That was the explanation of many cases of paracusis. A number of years ago a French writer on the subject said that the lesion which was at the bottom of otosclerosis was in the medulla lying between the nucleus of the 5th and that of the 8th nerve.

Mr. SOMERVILLE HASTINGS said that he had been particularly interested in Dr. Gray's ideas on paracusis. The explanation suggested was the only intelligible one which he had heard. Reference had been made to the work which Gordon Scarff and he (the speaker) had done in 1926, using Tucker's apparatus, whereby an oscillating wireless valve produced a pure note. One of 520 vibrations was used for the most part, but it could be varied. They did not use a tuning-fork as the source of sound; as the disturbing sound they used an unclamped or unweighted tuning-fork of 72 vibrations. This sound could be put into the same ear as the test sound or into the opposite ear. On their telephones were thick pads of felt, so that when, for instance, the disturbing sound was turned on to the left ear and the right was being tested, it was impossible for the vibrations to have been carried through the skull and so have shaken up the ossicles on the right side, as predicated by the ordinary explanation of paracusis. The disturbing sound was tried on the opposite ear, as a sort of fool's experiment, and in 12 cases they had found that there was definite improvement in the hearing of the one ear by making a noise in the other ear. That was done many times, and in some cases marked improvement was established. In one case the hearing capacity in the right ear was doubled by the presence of a disturbing sound in the left ear. They recorded the facts, but did not suggest any explanation, and what Dr. Gray now said explained matters.

By means of such accurate records of otosclerotic cases a knowledge of this disease ought to be built up. It was now time that this Section adopted some definite classification—based, it might be, on clinical symptoms—of otosclerosis, so that when otosclerosis was spoken of the speaker and the hearer might have in mind a definite picture of what was meant.

Mr. E. WATSON-WILLIAMS asked whether these were definitely cases of otosclerosis? The characteristic feature of otosclerosis was ear deafness, whereas one would expect a patient with such extensive degeneration of the nerve as that shown to have the signs of nerve deafness. Did these patients suffer from paracusis? *A priori*, one would expect that if nerve impulses overflowed from one nerve fibre to another, say from a fibre conducting a continuous noise-sound into one conducting conversation-sound, it would be more difficult, rather than less so, to distinguish the finer modulations on which depended the appreciation of speech. He would like to ask whether there was any regional distribution of the degeneration in the first case; for example was it central? [Dr. GRAY: Yes.] This was interesting, as he had often observed that the loss of hearing in otosclerosis was absolute for very low tones, that is, it was a nerve deafness.

Mr. A. LOWNDES YATES said that Dr. Gray had placed an entirely new view of paracusis before the Section, and so brought into line what had previously been divergent views. There was the possibility in many cases of a false paracusis, i.e., the patient did not hear the noise. There was also a type which could be called a "flush" paracusis. Any noise caused congestion of the vessels of the tympanum; one did not know if it also caused congestion of the vessels of the internal ear, though this was possible.

If a patient heard better in a noise and had true paracusis, that capacity to hear better continued after the noise had ceased for a varying time, which might be short or might be much prolonged. If one placed a strongly-sounding apparatus near an ear which was the seat of paracusis one could experimentally cause such a patient to feel that he was hearing better. Such improvement lasted for a time, and then the hearing relapsed to its former standard. Many reports of benefit to hearing from what were in effect noise machines, were due apparently to this temporary improvement—the result of "flush paracusis." Flush paracusis appeared, however, to be present in other conditions besides otosclerosis. In the case under discussion the diagnosis of otosclerosis was established by microscopy.

During life a certain number of cases which were clinically similar showed signs of former inflammatory changes in the middle ear. Was it not possible that if there was a lesion of the membranous periotic capsule, a slight inflammatory change might cause a good deal of mischief in the region of the round window or the oval window, leading to the type of deafness known clinically as otosclerosis? There must be many conditions of deafness clinically classified as otosclerosis in which one had no proof that there was any lesion of the bony periotic capsule until the patient died and the ear had been submitted to microscopic examination. In some of these, nerve changes might not yet have produced the lesions of the bony periotic capsule. Dr. Gray's observation formed a definite and important addition to knowledge of the ætiology of otosclerosis.

Dr. ALBERT GRAY (in reply) said that Sir James Dundas-Grant was right when he referred to the raising of the voice in order to be heard. Some were not true cases of paracusis at all; other sounds did not disturb them so much as they disturbed normal people. But in cases such as those mentioned by Mr. Somerville Hastings, and most others in which that factor did not enter, it seemed that there was a relative increase.

Otosclerosis was a manifestation of changes in which there was a certain general uniformity in the clinical and pathological pictures. But cases of otosclerosis differed from each other a good deal in minor details, and these differences depended on the extent to which the symptoms were due on the one hand to changes in the capsule of the labyrinth with fixation of that part, and on the other hand to changes in the nerve. All the changes, he contended, were degenerative and never inflammatory. If the results affected the oval window the ordinary otosclerotic type ensued, but in other cases types were found which were like the nerve type which Manasse described. In the latter case the patient was examined clinically, and after death the bones were examined. At the examination there was found fixation of the stapes on one side, while on the other it was a pure nerve deafness. A common but unknown origin was therefore present. He, the speaker, considered that the cause was related to the nutrition of the tissues.

With regard to Mr. Watson-Williams' remarks, the nerve impulses were added to by the disturbing noise. He reminded Mr. Watson-Williams that the axis cylinders were still functioning, and if the disturbing noise was a loud one the nerve-current was at a higher tension, and the axis cylinder which had the lower tension would receive nerve impulses from that of higher tension. The changes first appeared in the central part of the nerve. The fibres from the upper part of the cochlea came down in the core of the modiolus, and the other fibres were wound round like cotton on a spool.

In answer to Mr. Lowndes Yates' remark as to paracusis lasting after the sound was removed, he, Dr. Gray, thought that was due to the stimulating effect of the vibrations, such as occurred in the use of Noebel's apparatus. Active congestion in the vessels of the labyrinth certainly helped the hearing, and one was familiar with the effect of nitrate of amyl. He did not see how changes in the oval window and round window would affect the paracusis.

Two Cases of Endothelioma of the Middle Ear.—LIONEL COLLEDGE, F.R.C.S.

(I) A man, aged 43, was admitted to St. George's Hospital on March 9, 1931, under the care of Mr. Ivor Back. Below the right ear was a tender swelling, which was incised by the house surgeon and pus was evacuated. Examination later showed a foul purulent discharge from the meatus and granulations obscuring all view of the tympanic membrane. A probe passed from the opening in the neck upwards through the floor of the meatus. There was deafness of the middle-ear type. The patient did not wish anything further done and was discharged. He was re-admitted on October 11, 1931, in exactly the same condition. A radical mastoid operation was performed on October 14. The granulation tissue appeared to be of an unusual consistence, tough and gritty, so was kept for examination and the post-aural wound left wide open. The tissue appeared also to have invaded the inner end of the skin of the meatus, and the skin in this region was excised. Dr. John Taylor reported that the tissue was microscopically myxo-endothelioma and identical with a parotid tumour. On November 16, in view of the report, the cavity was widened still further, curetted, and covered with a Thiersch graft. No communication with the parotid gland was found. There has been no further sign of growth, and at no time has there been any facial palsy, nor has there been any evidence of a parotid tumour.

(II) Male, aged 66, came to St. George's Hospital complaining of a painless discharge from the right ear of uncertain duration. The meatus was occupied by a large aural polyp bathed in pus. There was deafness of middle-ear type.

February 10, 1932.—Radical operation: Some of the mastoid cells contained only mucus, but the ossicles were necrosed. The wound was left wide open behind. The operation has been followed by a partial facial palsy. The polyp and granulation tissue were sent for examination and Dr. John Taylor reported endothelioma. The section exhibited shows a typical endothelioma.

Auditory Nerve Tumour.—T. B. JOBSON, M.D.

Mrs. E. G., aged 63, domestic servant. Came to hospital on February 17, 1932. Deafness in right ear noticed twenty years ago. Very marked for three years, now total. Facial paralysis (right) one year. Tinnitus severe, continuous. Vertigo: daily attacks, falling forwards, no loss of consciousness. Nystagmus: slight spontaneous. Right frontal headache. No vomiting. Pupils equal and react to light. Eye movements normal. Optic discs show ? some blurring of E. and N. edges on right. Knee-jerks normal. No Rombergism. Blood-pressure 210. Tongue and palate move freely. Tympanic membranes are mobile and slightly opaque and show no evidence of suppurative disease.

Hearing: Does not hear a shout in right ear with Bárány control. C. V. left = 2 ft. Weber lateralized to right. C. 256 heard on right mastoid but not C. 128, 64 or 32. Cold caloric test produces no response in 2½ minutes.

A stereoscopic skiagram does not show any erosion of the temporal bone. Further radiograms are being made. This case shows the very slow onset and the classical symptoms of deafness, tinnitus, vertigo, ataxia, nystagmus, dead labyrinth and paralysis of seventh and eighth nerves.

I am indebted to Dr. Stanley Whitton and my colleague, Dr. A. F. Treadgold, for permission to show this case.

Herpes Zoster Oticus, with involvement of the Vestibular Nerve.—N. ASHERSON, F.R.C.S.

Patient, a girl aged about 10, complained of severe pain in the left ear, with some tenderness over the mastoid process. The temperature was slightly raised. Five days later complete facial palsy suddenly developed; coincident with this, a serous bleb appeared on the tympanic membrane. This bleb rapidly disappeared, leaving the membrane normal again.

Within thirty-six hours of onset of palsy, giddiness, ataxy and vomiting ensued. Coarse horizontal rotatory nystagmus to right; none to left (the affected ear). Pain no longer present. No pyrexia at any stage. No hyperacusis: hearing practically normal. No disturbance of sensation on side of tongue.

The case was admitted as one of acute mastoiditis. A single line of herpes developed on the face, running from the angle of the mouth towards the ear. This eruption faded two days afterwards. The labyrinthine symptoms subsided first, and the facial palsy had disappeared by the tenth day from its first appearance. The nystagmus could be elicited as before.

Six weeks later: still some slight nystagmus on looking away from the affected ear.

Specimen of a Temporal Bone, with Pus in the Mastoid Antrum, from an Infant dying from Diarrhœa and Vomiting.—N. ASHERSON, F.R.C.S.

The infant had diarrhœa and vomiting for fourteen days, and was referred for aural examination by Dr. D. W. Winnicott. Examination of the right ear showed a tympanic membrane slightly sagging and very little different from the normal membrane. Incision revealed pus. The child took its first feed for ten days without vomiting, after this. Within a few days the symptoms recurred. The other ear, on myringotomy, revealed pus also.

A Mastoid Operation performed through a Meatal Incision.—C. I. GRAHAM, F.R.C.S.

Mr. B. A. D. L. had an operation for acute mastoiditis on February 3, 1932.

The incision consists of two limbs meeting at an obtuse angle at a point one quarter of an inch within the meatus on the posterior wall. One limb is vertical and is carried upwards through the crus helicis, the other limb is directed backwards and slightly downwards in the lower part of the cavum conchæ. The incision is carried to the bone and the triangular flap is raised from the bone and retracted backwards. The operation is performed by the usual method, and the flap is allowed to cover the posterior wall of the cavity, after removal of a piece of the cartilage, and is retained in place by a single suture passing from the apex of the flap to the skin in the post-auricular groove.

CORRIGENDUM.

Page 883 (Sect. Otol. p. 83), remarks by Sir James Dundas-Grant (in discussion on paper by Dr. J. Kerr Love entitled "Towards the Prevention of Deaf-Mutism: A Review of Forty Years' Progress"), line 14:—For "aphasia" read "aplasia."

Section of Comparative Medicine.

President—Dr. J. A. ARKWRIGHT.

[*February* 24, 1932.]

DISCUSSION ON MILK FEVER, OR HYPOCALCÆMIA IN PARTURIENT COWS AND SIMILAR CONDITIONS IN OTHER ANIMALS AND MAN.

Dr. J. Russell Greig (*Moredun Research Institute, Edinburgh*): The pathology of the disease in cows known as milk fever, like that of eclampsia in woman, to which it bears some clinical resemblance, has long been obscure and, indeed, like eclampsia, it has become known as the "disease of theories."

As is well known, the disease usually attacks milk cows during the first seventy-two hours after parturition, which, almost invariably, has been easy and uncomplicated. The symptoms are those of excitement, accompanied by tetany of the limbs, especially of the hind limbs, followed by convulsive seizures. These in turn are succeeded by coma.

In 1897, J. J. Schmidt, a Danish veterinary practitioner, made the remarkable discovery that injection of fluids into the mamma effected prompt and complete cure. Mammary injection has to-day been replaced by inflation of the mamma, and as a result of this treatment the mortality has been reduced from 60 or 70% to less than 1%, but the action of mammary inflation in bringing about this remarkable result was, in its turn, quite obscure.

In 1924, Dr. H. Dryerre and I undertook the investigation of milk fever, and, after a study of all the available evidence, formulated the following working hypothesis:—

(1) The nature of milk fever may be understood as a parathyroid deficiency, resulting in the accumulation of toxic substances such as guanidine, and a fall in blood-calcium, the fall in calcium being further accentuated by lactation.

(2) The curative effect of mammary inflation is due, we supposed, to either (*a*) the stimulation of adrenal secretion and the consequent oxidation of toxins, or (*b*) the increased intramammary pressure causing a retardation of the formation of milk and consequent prevention of further transference of calcium from the blood to the milk.

(3) We further suggested that the well-known preventive value of a restricted withdrawal of milk from the udder after calving is probably due to this procedure, conserving the concentration of calcium in the blood.

If our conception of the nature of the disease was correct, then it followed that the blood-calcium in milk fever should be below normal. Analyses of seven samples of blood from as many cases of milk fever showed an average of 4·8 mgm. calcium per cent. serum: a marked reduction when compared with the normal—9 mgm. to 11 mgm. per cent.

While our subsequent work has amply confirmed our original view that acute calcium deficiency was an important factor in the production of the disease, there is now reason to doubt that the accumulation of guanidine bases plays an important part in its causation.

Again, our original view that mammary inflation possibly stimulated the secretion of adrenalin may now be abandoned in view of the carefully conducted experiments of Auger, who was unable to note any rise in blood-pressure following inflation of the udder.

Later in 1925, Little and Wright published the results of investigations carried out by them, and showed that the blood-calcium content of twelve cows suffering from milk fever was markedly low; that the degree of the fall in calcium concentration corresponded with the severity of the case, and that after recovery the calcium had again reached the normal range. Sjollema, Fish, Söderland and others have confirmed the association of acute hypocalcæmia with the disease.

From our subsequent work, we are now of opinion that acute calcium deficiency is not a mere concomitant of the disease, but represents its essential pathology, and that the curative action of inflation of the mamma is due to its restoring the blood-calcium to normal. These conclusions are based on the following considerations: (1) Milk fever is invariably associated with an acute hypocalcæmia. (Approximately 100 cases examined.) (2) The more severe cases correspond with the lower calcium values. (3) The fall in calcium is approximately coincident with the appearance of the symptoms. (4) Tetany is a symptom in severe cases of milk fever and the occurrence of tetany is recognized as consequent upon pronounced hypocalcæmia. (5) Mammary inflation raises the level of blood-calcium in a normal lactating animal. (6) Mammary inflation elicits a marked rise in the level of blood-calcium in milk fever and cures the disease; the process of cure, as manifested in the disappearance of the symptoms, corresponds with the rise of the blood-calcium. (7) Injection of calcium, exclusive of other treatment, raises the blood-calcium concentration and cures the disease. (8) Milk fever in cows, lambing sickness in ewes, and transit tetany in mares are all rapidly cured by mammary inflation and these are the only conditions in an examination of over 500 samples of blood in which an acute hypocalcæmia has been found.

We have no definite information to offer upon the cause of the calcium deficiency. It is known that colostrum is very rich in calcium, and the calcium lost in a single daily lactation is much more than that which exists in the blood at any given time. During lactation there must therefore be a very rapid mobilization of calcium from the skeletal deposits, and unless the parathyroid be active, this mobilization cannot be accomplished.

Nor do we definitely know the action of mammary inflation in restoring the calcium level. As indicated, it may be due to the increased intramammary pressure preventing further transference of calcium from the blood to the milk. It is also conceivable that the mammary distension squeezes back into the blood the calcium concentrated in the gland acini.

Lambing sickness, a disease in parturient ewes, has long been suspected of being allied in its pathology to milk fever, but since the pathology of milk fever was unknown, such possible relationship could only be conjectured. On its becoming clear that in milk fever we were dealing with a hypocalcæmia, we turned attention to the concentration of blood-calcium in lambing sickness and found, in a limited number of cases, that a similar condition was present in lambing sickness to that which obtained in milk fever (confirmed by Sjollema). It has also been found by Montgomery, Savage and Dodds that the disease in mares known as transit tetany is associated with a low blood-calcium. In both lambing sickness and transit tetany, inflation of the mammæ or injection of calcium appears to be equally effective.

Bosworth and Glover reported the result of treatment of seven cases of lambing sickness with calcium gluconate (20 gramme doses). They failed to obtain any curative response. These findings did not correspond with our experience, and Sjollema reports the results in 40 cases of lambing sickness treated by intravenous injection of calcium chloride. Of these 40 cases, 34 recovered promptly and completely within a few minutes after the injection. In some of the 6 cases in which the animals died, the injection of calcium was followed by immediate recovery, but death occurred during the night, presumably during a relapse.

Bosworth and Glover had one case in which the blood-calcium concentration

was 10·6%, but this case also showed a high protein nitrogen, and was presumably "pregnancy-toxæmia."

In 1929 I pointed out that this disease, "pregnancy-toxæmia," was commonly confused with lambing sickness, but can be distinguished from it on the grounds that in "pregnancy-toxæmia" the blood calcium values are normal, and Sjollema suggests that those cases in which calcium injection does not effect cure, probably represent some condition other than lambing sickness. Sjollema's figures for calcium in lambing sickness correspond with our own. He also finds that inorganic phosphate tends to fall, while the magnesium tends to rise. These findings correspond to his findings in milk fever in the cow.

There is now strong evidence that milk fever in the cow and lambing sickness in ewes represent the same disease.

Conditions clinically resembling milk fever in the cow and lambing sickness in the ewe are also met with in the parturient goat, the sow and the bitch. We have not had an opportunity of determining the calcium concentration in these conditions, but because of their clinical resemblance to milk fever, and because of their immediate response to both mammary inflation and calcium injection, it is reasonable to assume that they represent parturient hypocalcæmia in these animals.

Since, then, we have evidence that an acute parturient hypocalcæmia occurs in practically all the domestic animals, and since this condition represents a metabolic upset, as distinct from a specific infective disease, it is a reasonable assumption that a similar condition may occur in woman. I had long supposed that milk fever in cows might be closely related to eclampsia in woman and was anxious to see mammary inflation applied in eclampsia. I was fortunate in this respect in enlisting the interest of Dr. Francis Brown, then of the Simpson Maternity Hospital in Edinburgh, now Professor of Obstetric Medicine in the University of London, but though inflation of the breasts was applied in severe cases of eclampsia, no curative effect was elicited.

I understand that the results of calcium therapy in eclampsia in woman have been irregular. Actually, the blood chemistry of eclampsia and milk fever present some striking dissimilarities.

A very interesting case is reported in the *British Medical Journal*, 1931, i, 395, by Dr. J. G. Kinninmonth. The case was that of a toxæmia of an unusual kind, arising during the puerperium. The symptoms bore close resemblance clinically to those of milk fever, and Professor Oldfield, of Leeds, suggested to Dr. Kinninmonth that mammary inflation should be tried. This was carried out with a sterile Higginson syringe, attached to an exploring needle, which was thrust well into the breast substance; the nipples were tied off with tape. (A similar procedure is adopted in the case of the bitch, an animal whose mammary gland anatomically resembles that of woman.) Following this treatment, the patient made a prompt and complete recovery. It is unfortunate that no calcium analysis was carried out in this case, but in view of the rapid recovery which followed mammary inflation, it is reasonable to believe that this procedure produced a specific effect. Dr. Kinninmonth suggests that it is unlikely that this case is unique. Some of the cases described in hospital reports as "coma without fits" he says are probably really cases of milk fever.

Although it now seems unlikely that eclampsia in woman is closely allied to milk fever in the cow, the possible relationship of eclampsia to a condition in the ewe known as pregnancy-toxæmia is, we think, worthy of comparative study, and the biochemical features of this disease will be discussed by Dr. Dryerre.

Professor H. Dryerre said that as milk fever in the cow was invariably accompanied by a deficiency in the blood-calcium, and as the relief of this deficiency cured the condition, investigations were now proceeding to see if the incidence of the

disease could be prevented. It was common knowledge that once a cow had suffered from milk fever, it was liable to attack at subsequent parturitions. He referred to one case of a cow which had contracted milk fever at each of its five previous calvings. On each of the four days preceding its next calving it received a dose of vetostelin, and the blood-calcium rose from a pre-treatment level of 10·5 mgm. to 12·5 mgm. on the first day after treatment, falling to 11·3 mgm. on the day before parturition. The cow calved uneventfully, and the blood-calcium on the four succeeding days was 7·3 mgm., 11·5 mgm., 10·6 mgm. and 10·6 mgm. respectively, per 100 c.c. serum. Whilst this case was suggestive, it would require many more similar observations before conclusions could be drawn.

A condition in ewes, known as pregnancy-toxæmia, might, he thought, be a profitable one for discussion, owing to its similarity in some respects to eclampsia. This condition was frequently confused with lambing sickness. The latter usually affected the ewe after the birth of the lamb, but pregnancy-toxæmia always occurred before parturition. Since it had been pointed out by Greig that in lambing sickness there was a deficiency in the blood-calcium, and that the condition was relieved by udder inflation or calcium therapy, this treatment had been adopted. Several failures had been reported, and he, the speaker, was convinced that these had been due to faulty diagnosis. In every case of pregnancy-toxæmia which he had examined, the blood-calcium was normal. Significant differences had, however, been found in the non-protein nitrogen and the plasma proteins, which were increased as compared with the normal; whereas the magnesium and the inorganic phosphorus were diminished. Although the symptoms in many respects resembled those seen in eclampsia, the blood-picture was different. In both diseases the blood-calcium was normal, and in eclampsia also the non-protein nitrogen might not necessarily be increased. In eclampsia, however, it had been shown by Ivanyi, Rodecort and Lingenmeier that there was an increase in the blood-phosphorus, whereas in pregnancy-toxæmia of ewes this constituent was diminished.

Professor E. C. Dodds: I should like to question two points: (1) How easily can animals of the horse and cow type be made to suffer from tetany? Our observations on Welsh mountain ponies showed that very severe tetany might develop through fright and hyperpnœa. (2) There does not appear to me to be any connection between milk fever in animals and eclampsia in women. The essential differences are the morbid histological appearances of the liver, kidneys, etc., in eclampsia, and also the fact that the blood-pressure is always markedly increased.

Mr. W. L. Little: Considerable interest has been taken in this condition since 1925 when, in conjunction with Dr. N. C. Wright, I reported that cows with milk fever showed a decided drop in their serum calcium. Since then a similar condition has been described in ewes and mares. As occasionally goats are attacked at the time of kidding with a similar condition to milk fever, they would probably show a hypocalcæmia during the attack. The cause of this hypocalcæmia is still debatable.

In cows this condition is known as milk fever, an unfortunate name, for in uncomplicated cases the temperature is normal or more often sub-normal; probably the name was given before thermometers were in general use, but it shows that the disease was thought to be associated with milk production. Cows are affected at or about the time of calving, and those giving a high yield of milk are the ones generally attacked, and it is unusual for a cow to be attacked before having her third calf, i.e., when her milk yield is generally at its height. In this country a large number of animals are fed from the time of weaning upon a diet which contains barely sufficient lime for their needs. This is not very remarkable when one considers that on some untreated pastures the herbage is found to contain only 5½ lb. of lime per acre, whereas when limed the amount can be increased to 112½ lb. per acre.

Heifers are often put to the bull before being full-grown; they therefore need lime for their own skeleton and also for that of their calf, and after calving a large quantity is required for the milk produced. The production of half a gallon of colostrum in a cow weighing 1,200 lb. would deplete her entire blood of calcium were there no reserve to be called upon, and it is not unusual for a cow after giving birth to her third calf to give 3 to 4 gallons of milk a day. There is therefore a great demand for lime by a cow which gives birth to a calf every year and gives each year 600 to 1,000 gallons of milk.

If during the first three years in the dairy a cow's diet does not contain a sufficient amount of lime, it is reasonable to suppose that her readily available reserves of this element will be by that time very low, and her metabolism would not be able to cope with the sudden great demand following the act of calving. In this connection there is a point which in my opinion has not received sufficient attention—it is the action of an excess of phosphates in the diet. It is accepted by some workers that if phosphates are given to an animal in a state of latent tetany (and it is probable that a number of cows are in this state), it will go into tetany. It is also stated that an excess of phosphates interferes with the assimilation of calcium. In this country the diet of most cows is fairly rich in phosphates. Superphosphate manures are largely used, grasses and mangolds are rich in phosphates, so also are most cereals and cakes. There is reason to believe that the phosphate content is high and the calcium low. Does this excess of phosphates interfere with the assimilation of calcium?

Two cases have recently come to my notice which are of interest here. A farmer noticed that when his dry cows were grazed on a certain meadow they very frequently developed milk fever after calving, but did not so frequently when grazed on other land. An analysis of the herbage of the suspected meadow taken during June showed 0·933% of lime and 0·550% phosphates; the percentage of lime is about normal, but that of the phosphates is high. On another farm, the land of which was deficient in lime, the cows were rather liberally fed with fish meal which has a high phosphate content, their serum calcium under ordinary conditions was, on an average, 7·32 mgm.% and a large number of milk fever cases occurred every year; after the fish meal was stopped the milk fever cases were reduced to almost nil and the serum calcium of the cows was found under ordinary conditions to be normal, 9 to 10 mgm. %. It is well known that on some farms milk fever is prevalent and on others it is never found.

Another thing which must interfere with the assimilation of calcium by cows is the way so many are treated during the winter months. In this country we are not overblessed with sunlight, and cows are often not allowed to benefit by the little we have, being housed in poorly lighted sheds for months at a time. The supply of green food during this time is also often limited. In this connection it is worthy to note that a large number of cases of milk fever are met with in the spring, although the fact that spring grass is a great milk stimulant must also be taken into account; perhaps all these factors have their influence. The serum calcium of cows shows a slight drop at the time of calving; dry cows usually have a serum calcium above 10 mgm.%; at the time of calving it may drop to 8·5 mgm.% and then rise to between 9 and 10 mgm.%, remaining fairly constant during lactation. It was thought that if this drop could by some means be controlled it might show a way to prevent milk fever.

The following methods have been tried: (1) Dosing with calcium salts before calving. (2) Dosing with calcium salts after calving. (3) Injection of "paroidin." (4) Irradiation with ultra-violet light. (5) Feeding cod-liver oil before calving. (6) Feeding cod-liver oil and calcium salts before calving. (7) Subcutaneous injection of calcium salts just after calving. Sufficient work in this connection has not been done to draw any definite conclusions; the best results were obtained by

feeding cod-liver-oil and calcium salts. The subcutaneous injection of calcium salts may ward off an attack of milk fever.

It seems that if we are definitely to prevent milk fever in cows they must be fed and treated in a rational manner throughout their life; it cannot be prevented by a few days' or months' treatment before the act of calving.

Post-mortem appearances.—Very little has been written upon this aspect of the subject, probably because nowadays the percentage of deaths is low and most of the deaths are from septic pneumonia and not milk fever proper.

In those cases in which the animal has died after a bad attack, especially if tetany has been severe, decided changes are found in the muscles; this was first noticed by Thos. Wilson in 1922 who described it as gangrene of the gastrocnemius. The affected muscles show an appearance of dry necrosis, there is extravasation of blood between the fibres, some of which are swollen, and other fibres have lost their normal striation. The kidneys and bladder often show small hæmorrhages.

The treatment of these cases to-day confirms the contention that the disease is a hypocalcæmia. The benefit of intravenous injections of calcium chloride in 10% solution is almost immediate; the animal improves during the injection and a few minutes after can sit up without support, and in a short time, in some instances only a few minutes, get on to her feet and walk.

My method now is to inject, as slowly as possible, into the jugular vein 100 to 200 c.c. of the 10% solution, according to the size of the cow and severity of the case, I very rarely give more than 250 c.c.

In 1924 when I first started this line of treatment I was strongly warned against the chance of producing hypercalcæmia. Consequently I started using what I thought was sufficient to raise the serum calcium from 5 mgm.% which is about the average in milk fever, to about 7 mgm.% which is the danger line; although this small amount always gave improvement there were relapses, so I have gradually increased my dosage. There does not appear to be any fear of causing trouble by a hypercalcæmia, for it is found that 150 c.c. of a 10% solution of calcium chloride can be injected intravenously into a normal cow without producing untoward results (Peskett).

In practice I find it advisable to inflate the udder after giving the intravenous injection. This reduces the tendency to relapses—which, owners, who are all conversant with the inflation treatment, do not like.

The giving of parathyroid extracts, irradiated ergosterol, or cod-liver oil is not at present recommended as a curative or prophylactic, unless calcium salts are given at the same time, for although they might relieve the symptoms or prevent an attack, they may do so at the expense of the skeleton and would render the animal more liable to attacks in the future.

Hypocalcæmia in puppies.—What are generally termed "puppy fits" are, I think, very often convulsions due to a hypocalcæmia and resemble spasmophilia in children. Unfortunately I have not been able to have any blood determinations for calcium made on these cases, but I find that a subcutaneous injection of colloidal calcium generally relieves the puppy, and a proper diet and attention complete the cure.

Mr. O. Stinson: In Westmorland there are two deficient soil areas: (1) Lime-deficient. (2) Phosphorus-deficient.

(1) *Lime-deficient area.*—Lambing sickness (now known as an acute hypocalcæmic condition) is common.

Method for the prevention of lambing sickness: (*a*) Feeding hay during the winter, in addition to grass. (*b*) Taking the sheep down from the deficient area (on the hills) to the less deficient lowlands, several times for a week during the winter.

(2) *Phosphorus-deficient area.*—Symptoms of aphosphorosis are seen in all cows

after calving, and sometimes in cows during the last three months of pregnancy. It is noteworthy that there is an excess of lime in this area, and here lambing sickness is unknown.

Post-Parturient Dyspepsia.

Synonyms.—Slow fever, low fever, storr, yellows, etc.

Definition.—A deficiency disease having an associated (secondary) acetonæmia.

Occurrence.—A disease more particularly of the North of England and Scotland (as observed in the British Isles).

Animals affected.—Bovines. The disease occurs in the great majority of cases from six days to eight weeks after calving and occasionally during the last two months of pregnancy. Commonly the first attack is after the third calf, but it is met with after the first. Occurrence is almost invariably during the winter time when the cows are indoors, and then mostly towards the end of the indoor season, i.e., April. Frequently recurs after subsequent parturitions.

Ætiology.—The designation "post-parturient dyspepsia" is a misnomer. More recently it has been associated by Hudson with retention of uterine fluids.

When the condition arises soon after parturition the natural discharges from the uterus are retained, but the author has satisfied himself that the association is secondary, since the discharges are in evidence with the specific treatment which is to be described. The disease may be seen associated with a catarrhal metritis, but the resulting auto-intoxication acts, in these cases, only as an aggravating cause in that calcium and glucose are used up, although they are urgently, and directly, needed for the cure of the primary condition.

Primary cause.—A deficiency during pregnancy or lactation.

Secondary causes.—Factors which speed up oxidation or which lessen the supply of oxygen, viz., high protein diet, exercise, cold, excess of carbon dioxide in the atmosphere.

Symptomatology.—Three forms.

(1) *Subacute form*—which may merge into the epileptiform type. Anorexia, constipation; temperature from 101° to 104°; micturition in small quantities; emaciation; an odour of acetone from the body; tail sometimes held tightly between legs; diaphoresis (more or less); suggestion of pica; stiffness of limbs on walking; moaning in some cases, suggestive of a mental or nervous condition since pain is absent; frequently partial paraplegia of the hindquarters; suggestion of icteric membranes; the relatively high milk secretion is out of proportion to the severity of the symptoms.

(2) *Nervous form.*—Acetone odour from the body; constant licking of a leg or the wall, sometimes accompanied by salivation.

(3) *Epileptiform type.*—May be epileptiform fits of sudden occurrence.

Treatment.—Subacute form in the lactating animal.

Milking *once a day* only will cure this condition in from a week to ten days. In the treatment of the average cow all secondary causative factors may obtain as usual, provided that the deficiency is being rectified by the above treatment. In a serious case, obviously, these secondary causes must not be permitted.

Nervous form.—Inflation of mammæ, followed by milking once a day for a week or more. Secondary causative factors can obtain.

Epileptiform type.—Inflation of mammæ, followed by milking once a day for a week or more. Secondary causative factors can obtain.

In the pregnant animal secondary causative factors are removed, and 4 lb. glucose administered *per os* daily if necessary, as long as pregnant.

Similarities between milk fever and post-parturient dyspepsia.

The first attack is usually after the third calf in both diseases.

By lessening the milk yield by inflation of mammæ in milk fever, and by milking once a day in post-parturient dyspepsia, the condition is cured.

Refraining from milking for forty-eight hours immediately after parturition usually prevents milk fever.

High protein feeding is a factor concerned in causation of both.

Chloral hydrate alleviates the symptoms in both diseases.

Both diseases tend to recur after subsequent calvings.

Dr. R. H. Paramore asked how, if hypocalcæmia was the essential condition of "milk fever," and was itself due to a parathyroid deficiency, the parathyroid deficiency was to be explained? Why should the parathyroid go wrong in the best type of milking cow, the one that should yield the greatest amount of milk and was, as a rule, a massive beast? This incidence, which simulated so remarkably closely that of eclampsia in woman—the occurrence of the disease especially in the best physical type of individual—brought the two diseases into line.

Thus milk fever, of extraordinary interest in itself, was of considerable importance to those interested in eclampsia. It was the mammary conception of eclampsia, a view based on veterinary experiences with milk fever, which had led him, the speaker, to a study of the literature, though he had not seen a single case. The remarkable statement—which at first reading seemed an incredible story—was that pumping up the udder with a bicycle pump caused in the great majority of cases the rapid restoration of the animals affected, a large percentage of which would otherwise have died, and did so often very rapidly, even within twenty minutes. How could it be explained?

Bredo's paper (1909) opened the door to a new conception of the disease. It was stated that from 30 to 35 litres of milk could be expected from cows liable to or which became stricken with the disease, whilst the volume of the blood was only 45 litres. Bredo attributed the disease to a hyposerohæmia, but the argument led the speaker to question where the fluid, &c., for the milk came from. The answer was that it could only come from the intestinal tract and thus through the liver. It was thus clear that in these animals a greater flow of blood through the liver than in cows remaining normal had occurred, and the conception of a contamination of the systemic blood with insufficiently changed portal blood as the essential cause of milk fever arose.

How, then, did mammary inflation act? It had been stated that Auger had shown that no rise of blood-pressure occurred as the result of the inflation. But it was a physiological fact that closure of a bed of capillaries invariably raised the blood-pressure. If Auger had been unable to find a rise of blood-pressure—which other authors stated occurred—it could only be that the blood had been forced to flow more freely through other channels. The argument pointed to the kidneys being affected in this way.

The remaining question was: How did the calcium therapy work? He, the speaker, accepted Professor Greig's results: but how were they to be explained? The paper by Lamson, Minot and Robbins, in which it was stated that the administration of calcium mitigated or prevented the effects of poisoning by carbon tetrachloride in dogs, indicated that the drug—the calcium—acted by affecting the liver. It was stated that lack of calcium causes a paresis or paralysis of tissue cells: thus, in milk fever the liver cells, as other tissue cells, must be disturbed. If calcium cured milk fever, it seemed to the speaker that it must do so by stimulating the liver cells—perhaps also kidney cells—to greater activity, whereby the auto-

intoxication, which appeared to be the essence of milk-fever, righted itself, so that the animal regained consciousness, was soon able to stand, and rapidly became well.

Professor G. H. Wooldridge said he could assure Dr. Paramore, who appeared to be rather sceptical about the startling changes from deep coma to consciousness and apparent recovery occurring in these cases of milk fever under certain lines of treatment, that he had himself frequently observed these remarkable changes in from 15 to 20 minutes. He instanced particularly a milch goat that had kidded in May and had been in regular heavy lactation up to the time of the dairy show in October, at which she was to compete. On arrival she appeared rather tired and exhausted, and this was thought to be due to the long journey (250 miles). In the course of the next two or three days she became considerably weaker and her milk-yield rapidly diminished. On the third day she became semi-comatose and seemed about to die from exhaustion—in fact, he, Professor Wooldridge, had given up all hope of her recovery. As a last resort and more as an empirical measure than otherwise, he inflated her udder, and in fifteen minutes she regained consciousness, raised her head and took a small piece of cabbage in her mouth. She was not at that moment able to feed, but in less than half an hour she had actually masticated the cabbage. This amazing recovery was directly comparable with these cases of milk fever occurring soon after parturition. A case like this made it difficult to believe that calcium deficiency was the primary cause of the trouble, because inflation in this instance could hardly restore the calcium balance at such remarkable speed when there had been little or no lactation for several days. With regard to Professor Greig's view that hypocalcæmia was the primary cause of milk fever, he, the speaker, was not yet convinced, although he accepted, without hesitation, that such a deficiency existed in milk fever. He believed that it was a result rather than a cause of the condition, especially in view of the fact that inflation of the udder produced more spectacular and more consistent results than did the administration of calcium salts by any channel. His own opinion was that the condition would ultimately prove to be a neurosis.

Dr. J. T. Edwards said he had found, on inquiry from the Imperial Dairy Expert, that milk fever was not unknown in India, although the milk yield of indigenous cattle was low, suggesting that the disease was not restricted to breeds of Western cattle evolved for high milk production. With regard to Mr. Stinson's view that the disease was prevalent on soils deficient in lime, it was his impression that in localities where the mineral deficiency was known to have caused severe outbreaks of osteomalacia among livestock over long periods, such as had been recorded by Per Tuff (1923) in Norway, the abnormal occurrence of milk fever had not been stressed. It seemed to him that if milk fever was due simply to a lack of calcium in the diet, it would become prominent as a local cattle affliction before a state of soil deficiency was reached that would bring about the severe constitutional disturbances seen in osteomalacia. He had, as a veterinary worker, some difficulty in accepting the view put forward by Professors Greig and Dryerre that the pathology of milk fever could be wholly explained on the basis that it was a hypocalcæmia. This theory that the disease was somehow connected with a disturbance in parathyroid function and calcium metabolism had been put forward by them (1924, 1925) before they had obtained the impressive collection of experimental evidence which they had recently obtained to support it. Meanwhile, for a time, the hypoglycæmic theory had held the field. This theory seemed credible from the researches of the Swedish workers, Widmark and Carlens (1925), who found lowered blood-glucose values in lactating cows, temporary hyperglycæmia after udder inflation, the onset of symptoms like those of milk fever after insulin injection, and rapid recovery from

natural attack of milk fever after intravenous injection of glucose. These findings seemed corroborated by Auger (1926), of Lyons, and received the support of no less an authority than Macleod (1926), who observed in a depancreatized bitch after parturition the onset of acute hypoglycæmia, with symptoms like those of bovine milk fever; this recalled the earlier observations of Bert (1884) and Porcher (1909) upon hyperglycæmia, with diabetes, after udder ablation. It was soon found, however, by the Moussus (1926), in France, and American workers (Hayden and Sholl, 1924; Hayden, 1925; Fish, 1927, 1928) that in natural attacks of milk fever there was usually no hypoglycæmia but, on the other hand, often a well-marked hyperglycæmia, and that the increase in blood-sugar caused by udder inflation was due to a reabsorption of lactose from the udder. It must now, therefore, be admitted that the hypoglycæmic theory had not been substantiated. Yet, though the existence of a state of hypocalcæmia in milk fever had been confirmed by other workers (Little and Wright, 1925; Sjollema, 1928; Fish, 1929), the probable mechanism of the immediate cure by udder inflation in the cow during an attack, when udder secretion seemed to be in abeyance, and the reported rapid recoveries after intravenous injection of glucose, or, as had been mentioned by Professor Wooldridge and Mr. Stinson, the less dramatic recoveries after the older method of treatment, with chloral hydrate, suggested that milk fever might be a complex process in which the observed hypocalcæmia was only a component or concomitant phenomenon.

Mr. A. L. Bacharach said that those who questioned the causal connection between hypocalcæmia and milk fever had not justified their doubts. Apparently all present agreed in accepting a statistically valid association of the two conditions, for Professors Greig and Dryerre had furnished incontrovertible evidence on that point. Hypocalcæmia might be due to one or more of a number of different causes; the method of prophylaxis or cure must consequently vary. In experimental work on rickets, hypocalcæmia was susceptible of treatment by calcium therapy (subcutaneous or oral), phosphorus therapy, vitamin administration, parathyroid administration, irradiation, or even ingestion of ammonium chloride. It was perfectly possible for actual or potential hypocalcæmia to be the fundamental cause of milk fever, and yet for different dietary and other environmental factors or even pathological conditions to have caused the hypocalcæmia. That was probably why cases of milk fever did not invariably respond to calcium therapy, for example. Moreover, an excessive hypercalcæmia was practically impossible to produce in normal subjects (cf. Stewart and Haldane; Havard and Hoyle; and others), and this was only to be anticipated on physico-chemical grounds. Methods which failed to increase normal blood-calcium more than from 10% to 20% might have a far greater effect in severe hypocalcæmia.

Professor Greig, in reply, said that whatever work he had done in the investigation of milk fever had been done in conjunction with his colleague, Dr. Dryerre.

The symptom of tetany was common in milk fever, but in a number of cases the symptom did not occur, or was manifested in so mild a form that it was not observed.

Unlike Mr. Little and Mr. Stinson, he had so far failed to find any constant correlation between dietetic factors and the occurrence of the disease. Since the cow contained in her bones much greater supplies of calcium than were required by the soft tissues at any given time, one had difficulty in conceiving how dietetic deficiencies could play any important part in the causation of the disease. In his conception, the fault lay not in an absolute deficiency of calcium in the body, but in the inability of the calcium-regulating mechanism to mobilize quickly enough

from the bones the calcium requisite for the needs of the soft tissues during the crisis represented by the onset of lactation.

Mr. Stinson's reference to the use of chloral hydrate in the treatment of milk fever previous to the discovery of mammary inflation, raised an interesting point. There was a consensus of clinical opinion that this treatment was of distinct value, although the administration of large doses of a powerful narcotic to a comatose animal seemed quite irrational, and therefore the effect of chloral hydrate on the concentration of blood-calcium called for investigation.

He understood Dr. Paramore to suggest that the cause of the disease might be found in central necrosis of the liver, which had been shown by Lamson, Minot and Robbins to be associated with calcium deficiency. The rapidity and completeness of the recovery following mammary inflation or calcium injection, however, seemed to negative the view that the pathology of the disease was intimately associated with organic damage.

Dr. Edwards had mentioned that it had been reported to him that milk fever was not uncommon in India among cows possessing poor milking qualities. That did not correspond with his, the speaker's, information. He understood that the disease was very rare in India.

The hypoglycæmic theory, which was introduced by Neefs in 1923, was very attractive, and had been supported by numerous authorities, including Widmark and Carlens, Porcher, and Auger of Lyons. Although it was impossible to discuss the matter at that time, he had no hesitation in stating that, in consideration of all the experimental evidence, the hypoglycæmic theory could now be definitely abandoned.

Professor Wooldridge had described a case of "delayed" milk fever in a goat which had kidded five months previously. The milk secretion had markedly diminished, and shortly before the onset of the symptoms the animal had been travelled for some distance by road. That last observation was of considerable importance, as he, the speaker, had previously noted that forced exertion appeared to play an important part in precipitating attacks indistinguishable from parturient milk fever in both cows and ewes at various periods throughout lactation. These attacks also responded promptly to mammary inflation, and their pathology was presumably closely allied to, if not identical with, parturient milk fever.

As had been mentioned by another speaker, lactating cows at grass were frequently attacked by a condition indistinguishable from parturient milk fever, and these cows also responded promptly to mammary inflation. These attacks, in almost every case, had occurred during œstrum. He, Dr. Greig, entirely agreed with this observation. In another place he had pointed out the association of œstrum with the condition and had offered as an explanation the fact that ovarian secretion was known to be capable of lowering the concentration of blood-calcium.

Professor Wooldridge had said that we were not yet near the solution of the actual cause of milk fever. With that statement he, Dr. Greig, both agreed and disagreed. He believed that, upon the evidence submitted, it was justifiable to conclude that the immediate cause of the attack was an acute hypocalcæmia. He could not, however, do more than offer a plausible explanation of the cause of this hypocalcæmia. There was no experimental proof that it was due to one cause or to another, but if he had been able in this discussion to produce incontrovertible evidence that the cause of the hypocalcæmia was, say, parathyroid deficiency, they might reply: "Agreed, but what is the cause of the parathyroid deficiency?" If he then were able to produce unassailable evidence that the parathyroid deficiency was, in turn, due to deficiency of vitamin X, they could say: "Agreed, but what is the cause of the vitamin X deficiency?" He was content to take one step at a time. He believed that, in consideration of all the evidence, the essential pathology of milk fever had been demonstrated in an acute hypocalcæmia. The investigation of the causes of that acute hypocalcæmia lay in the future.

Professor Dryerre, in reply, said it was undoubtedly the case that inflation of the udder produced a rise in the blood-calcium. This had been experimentally demonstrated by Greig and himself on lactating ewes, and it had been observed by blood examinations on cows recovering from milk fever, which had been treated only by mammary inflation. The question had been raised as to the source of this calcium. It would be premature at this stage to say definitely that it came from the mammary gland cells, but an observation made by Hayden and Fish was at least significant. They found that after inflation of the udder lactose was present in the blood, and there was none there before inflation. It was a specific function of the mammary cells to manufacture lactose, and if it were possible to "squeeze" this product back into the circulating blood, it was conceivable that the accumulated calcium might suffer a similar fate. The question had been raised as to why the injection of calcium salts brought about recovery, even when the blood-calcium content was still much below normal. In his opinion this was due to the sudden accession of calcium to the blood. It was the steepness of the gradient of application which was effective, rather than the absolute amount of calcium present. He instanced the analogous condition in the application of an electrical stimulus to an irritable tissue. A slow, gradual increase in the strength had no effect, whereas sudden small steps produced a response. One speaker had remarked that he knew of cows suffering from osteomalacia, and wondered why they did not develop a condition like milk fever if this were due to a calcium deficiency. He, Dr. Dryerre, would point out, however, that in osteomalacia there was no deficiency in the blood-calcium. With regard to the hypoglycæmic theory, he considered that this had now outrun its usefulness. His own findings, in accordance with that of most other workers, had shown that in milk fever the blood-sugar content might be above, below, or on a level with the normal, and bore no relationship to the severity of the condition. He suggested that the curative effect of the injection of glucose might bear some relation to the known property of glucose solutions of increasing the solubility of calcium compounds.

Section of Dermatology.

President—A. M. H. Gray, C.B.E., M.D.

[*March* 17, 1932.]

Collagenous Degeneration : Case for Diagnosis.—H. C. Semon, M.D.

The patient, a man aged 36, was first seen at the Royal Northern Hospital, February 3, 1932, on account of an eruption on the trunk, upper arms, and thighs, which he said had been present for about seven months. There have never been any subjective symptoms.

There is only one type of eruption present, and its elements can be analysed only at the spreading margins, and best perhaps on the buttocks and thighs. Elsewhere they have become conglomerate, and are so faintly marked as to defy description. On the base of the neck and over the pomum adami, where the signs of it were first noted, the condition has entirely involuted, leaving a remarkable inelastic texture, as seen temporarily after œdema of the skin, or in old age.

Each lesion is oval in shape, its long axis—about a quarter to half inch—being disposed horizontally. A delicate mauve is the prevailing tint of the more recent lesions, but where they have become absorbed into the sheet-like agglomeration on the trunk the colour is brownish. Here too all the follicles are rendered extremely prominent by the apparent exudation, and almost pin the epidermis down like "buttons on a mattress," and at a few feet produce the appearance of coarsely grained leather. The individual small elements are smooth, raised but scarcely palpable lesions. There is no scaling, or other change suggestive of a disturbance of the Malpighian body. The general effect is one of œdema or exudate into the epidermis, and of perifollicular distribution.

A lesion excised and submitted to Dr. Ellison for a histological report presented the following features :—

"The epithelial layer is for the most part flattened owing to the disappearance of the rete cones. The collagenous tissue arises immediately beneath the epidermis and is relatively a-cellular; its bundles are indistinct, suggesting the effect of ground glass, under a ⅔ objective, and stains poorly with v. Giessen. The elastic tissue on the other hand is well presented by Weigert's stain and presents no evidence of degeneration. The appearances suggest a form of collagenous degeneration of the skin."

No other abnormalities were discovered during this patient's visits to the out-patients' department. The circulatory and nervous systems were healthy, and the Wassermann reaction was negative. A blood-count was normal.

A form of "collagenous degeneration" is the only diagnosis that can be suggested at the present time, but progress will be watched and the patient will be shown again at a future meeting of the Section.

Granulomatous Eruption in an Infant : Case for Diagnosis. H. HALDIN-DAVIS, F.R.C.S.

The patient is a healthy baby aged eight months who since about last Christmas has developed a number of lesions on the calves of both legs and a few more on the scalp, and a single one on the left cheek. The lesions on the calves consist of irregularly shaped areas, slightly raised above the level of the surrounding skin, rough on the surface, and of congested appearance. They might well be described as granulomata without any actual pus formation. The lesions on the scalp and face were more crusted, and deep-seated pustules were present beneath. For about two months the condition grew steadily worse, fresh lesions making their appearance on the calves and the old ones increasing in size, although a few of them began to involute. At no time did the baby's health suffer at all. It was taken into the Royal Free Hospital for a few days for investigation, a biopsy was made and a search was conducted for any form of infection, either bacterial or fungoid. Nothing whatever was found. The section showed considerable thickening of the epidermis with considerable prolongation downwards of the papillæ, almost suggestive of an epithelioma. The diagnosis which immediately suggested itself was a bromide or an iodide eruption, but the closest inquiry failed to elicit the slightest historical support for this idea.

The doctor in attendance is emphatic that the child has never had either bromide or iodide. The only medicine which it has ever taken was a cough mixture which contained merely syrup of tolu and tinc. camph. co. Moreover, the child has always been looked after by its mother, who stoutly denies any use of teething powders or other infantile sedatives. However, since first seen at the end of February the condition has steadily improved and the eruption is now on the point of complete disappearance.

Dr. H. C. SEMON said that this was, almost certainly, a bromide eruption ; in his own cases of that condition the same areas had been involved as in this case. In adults, any cardiac or renal failure seemed to predispose to bromide.eruption.

Swelling and Discoloration of Lips : Case for Diagnosis.—ROBERT KLABER, M.D.

E. A. K., a nurse, aged 32, has for two and a half years had attacks of swelling and brown discoloration of the lips, occurring at irregular intervals. The upper lip is the more markedly affected and, as the condition subsides, a linear, light brown discoloration with slight scaling persists, especially at the mucocutaneous junction. No eruption elsewhere. No external irritant has been traced. Patient is otherwise in good health. She has lived for a year in Kenya, and for eighteen months in the Argentine. The eruption was first noticed while on ship returning from Kenya.

Past History.—1929 : A brownish scaly rash on chest and shoulders said to be due to fungus. Cleared up after painting with iodine. 1931 : A small patch on left breast, which cleared up with ointment.

Investigation.—No fungus found.

Tinea Versicolor of the Trunk and Groins Simulating Erythrasma.—C. H. WHITTLE, M.D., M.R.C.P.

F. C., aged 30, male.

History of five years' slowly developing patches of discoloration in the groins and on the trunk : itching. He customarily wears the same vest at night as during the day time. He has been married several years and his wife is unaffected. When first seen the lesions were much darker red than at the present time, and in the groins strongly suggested erythrasma. Now they are a yellowish brown and more typical in colour. The changes in colour in this condition possibly suggested the origin of the name " versicolor."

Scrapings put up in potash and examined microscopically are full of the fungus microsporon furfur.

In places the condition is still rather suggestive of erythrasma. I have been unable to get the organism to grow on the ordinary Sabouraud media. In the potash specimen [shown] there are many budding forms suggesting its near relationship to the monilia group. I do not know whether this is a common feature of this fungus.

Epidermolysis Bullosa with Cutis Hyper-elastica.—A. BURROWS, M.D.

The patient, a schoolgirl aged 14, seen at the London Hospital, in association with the mother, gives a history since birth of a flexible skin, which returned to normal when released, and of a particular susceptibility to injury over the bony prominences. The patient has always had cold, cyanosed hands, with a tendency to chilblains. When injured, the skin tends to do one of two things; either to develop large blister-like lesions, often with the formation of bruises, or it "splits right down to the fat," making a deep and ugly wound. In one case the patient had to be treated at the German Hospital for one of these wounds—in the left knee—which became septic. There are the scars of injuries over both knees and above the left shin, and the left forearm. The skin itself gives a silky, over-rolling feeling when palpated, and can be abnormally stretched. This feature is most marked at the elbows and knees, where, if stretched and released, the skin goes rapidly back to normal, almost as though it were elastic in nature. The elasticity is notable on both sides of the body.

The patient has lax joints, particularly noticeable in the thumbs of each hand, which can perform the usual "double-jointed" movements, and can be greatly hyper-extended. The patient, when she used to dance, could comfortably touch the back of her head with her heel. It is not quite so easy for her to do this now, but she can get her heel very near to the back of her head. Except in the finger and thumb joints and in one toe, however, laxness is not a marked feature.

The hands are blue and cold. The patient suffers from chilblains, but has only once had a broken one. The condition is less evident in the summer.

Family history.—Paternal grandfather died from dropsy, paternal grandmother is alive, but suffers from prolapsus uteri; maternal grandfather died of diabetes; maternal grandmother is well. The father suffers from high blood-pressure, with secondarily involved heart and kidneys. The eldest daughter volunteers the information that the father has double-jointed thumbs, which are "rather a feature of the family." The mother is living and quite normal. There are four children. The eldest, a girl aged 22, is well, and has no chilblains and no elasticity of the skin, but shows a laxness of the joint of the left thumb, which can be markedly hyper-extended. The second child is a girl aged 18, who suffers greatly from chilblains and blue hands and feet. The condition is controlled by calcium lactate. The third child is the present patient. The fourth child, a boy aged 10, is quite well. The mother had no miscarriages.

A number of references to this condition are scattered through medical literature. Erasmus Wilson in his "Lectures on Dermatology," 1874-5, under the heading "Abnormal Growth of the Integument, particularly the areolo-fibrous element," describes the case of Georgius Albes who had extreme elasticity of his skin. Erasmus Wilson gives John Bell as his authority, but this I have not been able to trace. Sutton ("Diseases of the Skin," 1931, vol. 1, p. 570, footnote) states that Turner was Wilson's authority. It appears that Daniel Turner who wrote a work "De morbis cutaneis" (1715-1736) describes Albes in his introduction. He was, however, a mere copyist and of no great repute. His authority was Job Janszoon Meek'ren, a notable surgeon of Amsterdam, who was a pupil of Tulp (the original of Rembrandt's "Anatomist"). A posthumous work of Meek'ren's was published in Dutch in 1668 and translated into Latin by Abrahamo Blasio in 1682. In Chapter XXXII of this

work a portrait of the Spaniard Georgius Albes is given, and it states that he regularly appeared before certain surgeons in Amsterdam. [A copy of the illustration was circulated at the meeting (see fig. 1).]

FIG. 1.—De dilatabilitate extraordinatiâ Cutis in viro quodam Hispano, "Observationes medico-chirurgicæ," J. Meek'ren, Amsterdam, 1682.

Turner writes as follows :—

"Of the wonderful of this part (skin) I have heard nothing that comes up to that in a young Spaniard Meekrin takes notice of (*Obs. Med. Chir.* Ch. 32) who in the Hospital at Amsterdam shewed himself to van Horn, Silvius, Piso, and other learned physicians; taking with his left hand the skin of the right shoulder and pap and bringing the same up to his mouth; again he would draw the skin of his chin down to his breast like a beard and presently put it upwards to the top of his head, hiding both his eyes therewith. After which the same would return orderly and equally to its proper place lying smooth as in any other person. After the same manner the skin of the right knee and leg he would pull either upwards or downwards for half a yard's length whilst (which was yet more remarkable) the skin of the left side could not admit any such extension."

It should be noted that the condition here was unilateral.

Erasmus Wilson also gives a case, rather less to the point, of a girl aged 17 with a condition called "relaxatio insolita et cutis pendula." The appearance in this case was like a "magnified cutis anserina." The integument hung in folds, and the patient, it should be noted, was subject from time to time to displacement of the patella.

Reference is also made to a quotation from Hippocrates respecting the Scythians, who were supposed to suffer from a similar condition associated with lax joints.

Gould and Pyles, "Anomalies and Curiosities of Medicine," 1897, quotes with an illustration the case of Felix Wehrle (1888) as an example of abnormal elasticity of the skin.

Later and more in line with our present case is described, by MM. A. Gilbert, Maurice Villaret and Grellety Boisviel, a patient who was sent to them with a diagnosis of "Acrocyanosis." In the *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris*, 1925, p. 303, the above authors set out the case as "une hyperélasticité congénitale des ligaments articulaires et de la peau."

This patient, a male, was aged 22 and looked younger; there was a complete absence of beard and moustache. He had cyanosis of the hands, feet and ears, which the mother said had existed from birth. She noticed, at the same time, laxity of the joints of the fingers and toes. The fingers could be turned right back, as also could the toes. The knees were affected, but the other joints appeared normal although the patient was of an abnormal suppleness. A skiagram of the distorted hand was shown. The skin over the body as a whole was thin and smooth. That of the hands was flabby and lax. The skin of the body, including the face, could be stretched out to a great distance and returned to normal, smooth and uncreased. The condition had no relation to the loss of elasticity shown in certain diseases.

Family History.—The mother married twice. She showed no abnormality. The father died from hemiplegia. There were nine children of this marriage. The first, a girl aged 24, suffered from cyanosed limbs and ulcerated chilblains, but nothing else. The second is described above. The third, a girl aged 20, from 18 years of age was very fat. She suffered from cyanosis of the limbs, elasticity of the joints of the hands, but no higher elasticity of the skin. The Wassermann reaction was negative. The fourth (11 months old) died from broncho-pneumonia. The fifth, a girl aged 19, suffered from acrocyanosis and ulcerated chilblains. The sixth, aged 14, and the seventh, aged 13, were both well. The eight and ninth were twins. The eighth died at the age of 4 months from athrepsia. The ninth was alive but had enlarged glands and rickets.

Of the second marriage there were three children, all alive and healthy. The authors practically disprove any influence of syphilis, and there was no one else in the village suffering from this condition.

The case I show to-day (figs. 2, 3 and 4) has a particular interest in tending to bring together a certain number of congenital abnormal manifestations, and at the same time illustrates Warner's law that congenital abnormalities are usually multiple. Some doubt seems to exist respecting the exact findings of the histological examinations of the skin of these cases of hyper-elasticity, but there appears to be little doubt that a defect or abnormality of the yellow elastic and the white connective tissue fibres is present. The balance between the two elements has not been worked out.

It is also of interest to remember that when the histological examination of the skin in cases of epidermolysis bullosa has been made, apart from the changes which are found in the immediate vicinity of the blisters, there has been on the whole a tendency to suggest that the yellow elastic and the white connective tissue fibres were at fault.

Connected with this might possibly be the condition "pseudo-xanthoma elastica," in which in small areas of the body the yellow elastic fibres are found to be longitudinally split or transversely fractionated.

It would seem, therefore, that hyper-elasticity should not be looked upon merely as a lesion of the skin or of the joints, as the case may be, but as a deficiency affecting all the connective tissue of the body as a whole, which defect may be universal, almost complete (with lax skin), incomplete (with hyperelastic skin or joints), or possibly localized.

In these circumstances we could probably gather together cutis hyperelastica,

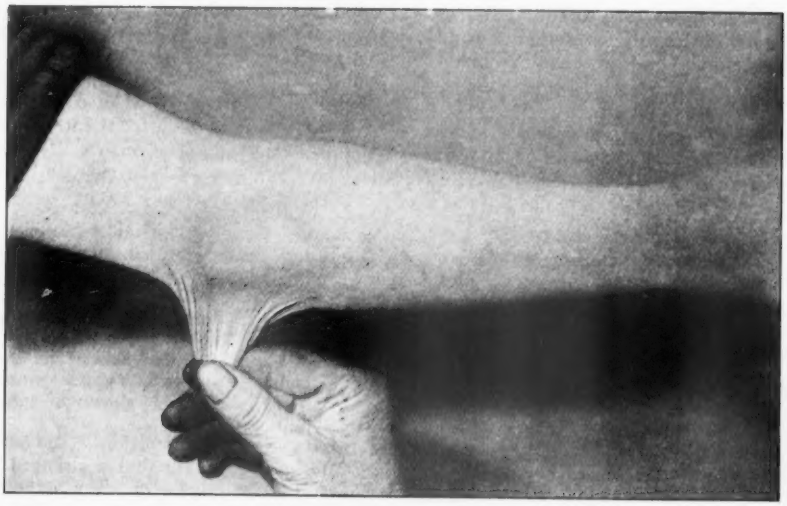


FIG. 2.—Elastic skin near elbow.

FIG. 3.—Epidermolysis bullosa—scars on knees.

lax or abnormally supple joints, and epidermolysis bullosa (india-rubber men, some acrobats, etc.), into a single group of congenital deficiencies of development of the connective tissue with different local manifestations.

At the same time we may also get a further idea of the ætiology of these conditions when the question of the cyanosis of the hands and chilblains is considered.

FIG. 4.—Hyperextension of digits.

Thus the foundation of the whole of these manifestations may be a defect of internal secretion with the corollary that internal secretion may control the development of connective tissue.

A histological report will be made later.

Drs. BARBER, KNOWSLEY SIBLEY, PARKES WEBER and DORE mentioned similar cases.

? Lichen Scrofulosorum : Case for diagnosis.—ARTHUR BURROWS, M.D. (for Dr. W. J. O'DONOVAN).

W. L., male, aged 22.

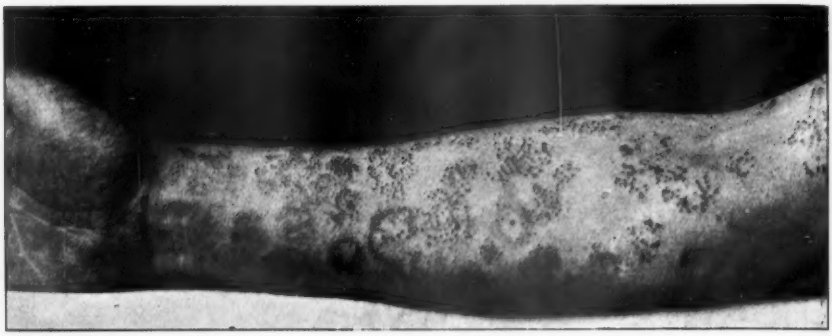
The lesion appeared suddenly, and is of one month's duration. The rash is present on the flexor surfaces of the forearms and on the legs. The scalp is free.

The skin presents non-irritating, well-defined cyclic aggregations of sparse, solitary pink papules, with filiform, horny, projecting spines. It gives a fine nutmeg-grater sensation to the hand.

The patient's general health is good and he presents no obvious signs of tuberculosis.

The histological report on the piece of skin removed for microscopic examination is as follows :—

"In the dermis are numerous small areas where dilated capillaries are surrounded by lymphoid cells and spindle cells. This infiltration is denser around two hair follicles, and around one of these some of the spindle cells are of the epithelioid type. There is one small



Dr. Burrows' case for diagnosis.

nodule in the dermis composed of a few epithelioid cells, a centrally placed giant cell, and a peripheral zone of infiltration with lymphoid cells.

"There are no conspicuous changes in the epidermis. The cells of its deeper layers are occasionally swollen and vacuolated and vague of outline where they are involved in some of the areas of dermal inflammation. The stratum granulosum is of uniform thickness. The stratum corneum is not definitely thickened."

Cornu Cutaneum Manus.—ARTHUR BURROWS, M.D. (for Dr. W. J. O'DONOVAN).

W.D., male, aged 54, gives a fifteen years' history of redness at the outer aspect of the palm of his right hand.

Dr. Burrows' case of cornu cutaneum manus.

Five years ago a crust began to form at the site and this came off from time to time. Four years ago a growth developed which in twelve months grew into a fine horn. This was knocked off. Two years ago the patient went to a London hospital

and the site of the horn was treated by a radium plate. The patient kept well, but did not attend further for observation and treatment, and six months later a growth recurred on the palm.

At present there is a double rough scaling area, one of which grows a horn about half-an-inch long. It is proposed now to treat the lesion by means of buried radon seeds.

Sarcoid.—H. MACCORMAC, C.B.E., M.D.

The patient, a woman aged 33, shows typical sarcoids of the Schaumann type. The lesions began to appear one year ago on the bridge of the nose, the right cheek and right shoulder, in the form of infiltrated, dark red, raised tumours. The right index finger shows marked swelling; skiagrams, however, failed to demonstrate any "clear areas." Both the von Pirquet and Wassermann reactions are negative. The microscopical appearances of a piece of the granuloma show a tuberculoid structure. The patient has been treated by novarsenobillon; five intravenous injections have been given with benefit, and it is proposed to follow up this treatment with sodium morrhuate, according to the technique suggested by the President.

The PRESIDENT said he found that novarsenobillon had a marked influence on this condition. The first case on which he used sodium morrhuate was one which did not clear completely under novarsenobillon, and with sodium morrhuate it cleared up completely; two years afterwards there was no trace of the condition; he had not seen the patient lately. With regard to the use of novarsenobillon and the tendency to recurrence, the same applied to sodium morrhuate. In the case of a patient he had shown at the meeting of the British Association of Dermatology in 1930, with continuous fever and a large spleen, the effect of treatment was remarkable, but when treatment was stopped the enlargement of spleen and the raised temperature recurred. He thought that the action of sodium morrhuate in sarcoid was like that of chaulmoogra derivatives in leprosy; the lesion was cleared up, but recurrences occurred.

Lichenoid Patches interspersed with Retiform Telangiectases: Case for Diagnosis.—Sir ERNEST GRAHAM-LITTLE, M.D.

At first I regarded the condition as an example of parapsoriasis lichenoides, the lichen variegatus of Crocker. The eruption consisted of large sheets of shining lichenoid patches, interspersed with retiform telangiectases. I am, however, prepared to accept it as a case of poikilodermia vasculare of Jacobi. The patient has suffered from the eruption for four years and every kind of treatment has been applied without avail.

Multiple Sebaceous Cysts, Recurrent since Infancy in a Middle-aged Woman.—Sir ERNEST GRAHAM-LITTLE, M.D.

The patient is aged 35. Her scalp is practically covered with discrete cysts from which ordinary sebaceous matter can be extruded through the central punctum. She has been troubled with them since infancy. In several instances the cysts have been excised but they have recurred.

Disseminated Hypodermic Carcinomatous Nodules.—Sir ERNEST GRAHAM-LITTLE, M.D.

The patient, a man aged 69, otherwise in good health, came a fortnight ago to St. Mary's Hospital on account of a large number of hard nodules, hypodermic in position, and showing no discoloration of the skin over them. They were very numerous but had all come out within three weeks. No enlarged glands could be felt.

On microscopical examination the subcutaneous tumour showed an adeno-carcinoma of very malignant type.

POSTSCRIPT.—Since the meeting this case has been admitted to Mount Vernon Hospital under the care of Mr. Stanford Cade, but as the patient is now showing deep jaundice, treatment with the 4-gramme bomb which had been suggested has not been applied, as offering no chance of amelioration.

Granuloma Annulare.—Sir ERNEST GRAHAM-LITTLE. M.D.

The patient, a woman aged 45, has typical lesions of granuloma annulare on both hands and nowhere else. There is a history of very numerous recurrences, some twenty-five to thirty within the last twelve years.

The histological appearances are also typical.

Superficial Scleroderma.—G. B. DOWLING, M.D.

C. B., male, aged 46. The condition began about ten years ago in the form of areas of reticular atrophy about the sacral and lumbar spine, on the chest and about the shoulders. He took no notice of these, but about four and a half years ago red irritable areas began to develop. These appeared in patches of irregular size and shape, on the buttocks, arms, legs, shoulders, abdomen, and back. He says that they were acutely inflamed, raised, and intensely irritable for about four or five days, when they subsided, leaving brown marks.

The attacks have occurred at irregular intervals, on an average about three times a year, in the same pigmented areas, though new areas have appeared from time to time, and have lasted almost always about four days. In October, 1931, following an attack of tonsillitis, the worst attack of all occurred; in this, intense burning and irritation were present, and on some of the lesions large blisters developed; the penis was also involved.

The most recent attack, which took place about six weeks ago, was very severe and lasted about a week.

He has been completely incapacitated during the attacks, and does not recover his normal health for several weeks as a rule. Altogether he has been away from his work for three months during the past year.

In addition to these attacks of erythema, he suffers constantly from flatulence and abdominal discomfort; but these symptoms have, I think, nothing to do with the cutaneous condition.

The lesions consist principally of moderately dark-brown areas, of irregular size and shape, distributed on the buttocks, back, abdomen, shoulders, arms, thighs and legs. The surface is in some places slightly scaly. In all these areas reticular atrophy can easily be observed; most of them, however, are situated on the outskirts of non-pigmented areas exhibiting a marked degree of reticular atrophy.

Apart from these pronounced lesions, there are widespread areas of lightly pigmented skin on which may be seen dilated venules in large numbers; these areas cover a good deal of the trunk and are especially prominent on the sides of the thorax.

Histological examination shows disappearance of interpapillary processes, follicles, and sebaceous glands, but no marked thinning of the epidermis as a whole. Slight thickening of the horny layer is also apparent.

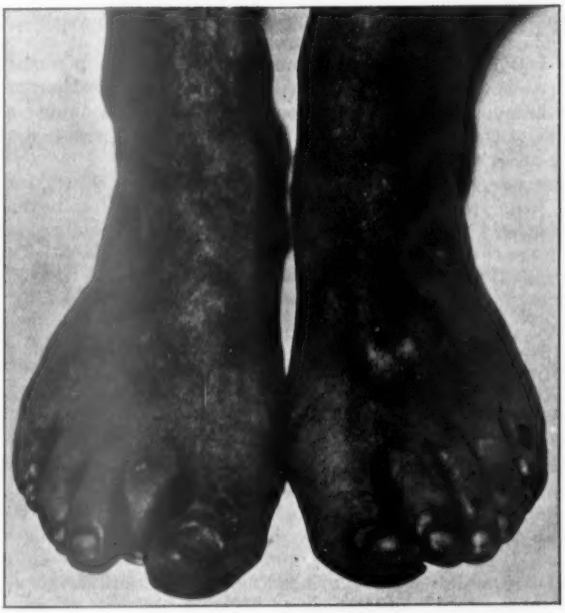
The elastic tissue is present in abundance in parts but in others it is diminished. There are a few small spaces in the connective tissue almost immediately subjacent to the epidermis which appear to be filled with fat cells.

THE PRESIDENT asked whether there was any question of tuberculosis in this patient. The case was somewhat like one which he (the speaker) had shown a few meetings ago, in a nurse who had had marked phthisis, which was not, however, very active at the time.

Dr. DOWLING (in reply): My original diagnosis was that of superficial scleroderma, but I had never observed reticular atrophy in this condition before, and ultimately made the tentative diagnosis of poikilodermia (Jacobi). From what I have learned to-day, however, it is evident that the former diagnosis is the correct one. The attacks of erythema with intense irritation and on one occasion bulla formation, must be very unusual. I think that the question of phthisis can be definitely excluded in this case.

Painful Redness of Feet from Arterial Stenosis, or more probably, Erythromélie (F. J. Pick).—F. PARKES WEBER, M.D.

The patient (A.W.), aged 35 years, an unmarried woman, rather thin, about ten years ago (1922) noted gradually increasing painful redness, often with lividity, of the left foot, at first limited to the left side, the commencement of which had been preceded by local pain. Both the redness and the pain were chiefly (almost only) present on standing or when the foot was in the dependent position. Later on similar phenomena appeared gradually in the right foot and became well-marked in the summer of 1931. The feet are usually cold and pulsation is absent in the left, but not in the right, arteria dorsalis pedis. In 1927 I thought that pulsation in the femoral artery at the groin was less on the left than on the right side, but now pulsation, though rather weak, seems to be equal on both sides.



This photograph (kindly taken by Dr. Weisswange in March, 1932) well shows the extreme engorgement of the cutaneous blood-capillaries of the patient's feet in the dependent position. The white mark on the dorsum of the left foot has been artificially produced by pressure applied just before the photograph was taken. Such anæmic white marks in this patient disappear almost instantaneously when the pressure is removed, even more rapidly than they do on the skin of normal individuals.

In April, 1925, Mr. A. E. Mortimer Woolf had performed femoral periarterial sympathectomy (or rather, Mr. Sampson Handley's modification) on the left side and had found that the femoral artery was very small. No alteration in the patient's symptoms resulted from the operation.

At present the phenomena in the feet are chiefly marked in the upright position, or when they are allowed to hang down, and are much less noticeable when the patient lies flat in bed. In fact, the phenomena in both feet are typically *erythromelalgic*. As soon as the patient gets up on to her feet, or lets them hang down, they both, especially the left one, become very red (partly livid) and painful.

This has been so since 1922 on the left side and since 1931 on the right side. But from the traditional classical picture of erythromelalgia these phenomena differ by the absence of excessive pulsation in the arteria dorsalis pedis; indeed, no pulsation at all can be felt in this artery on the left side.

There is a diffuse shiny appearance of slight cutaneous atrophy over the dorsum of the left foot, with exaggerated distinctness of superficial venules. The movements of the left knee-joint have been more or less limited since 1918, when she suffered from swelling of the joint (suspected to be tuberculous), following a local trauma. There is a history of "synovitis" of the right knee about 1913, lasting a year; and in 1931, after local swelling, the movements in the right knee-joint have become limited, as in the left. Radiograms of the patient's knees and legs taken in March, 1932, together with controls of the same age, show very little, if any, decalcification.

On the back of the left forearm, in the left axilla, and on the left side of the trunk are some achromic areas of skin, and there is partial canities of the left axillary hair. I should have been inclined to regard these pigmentary changes as ordinary vitiligo, but the patient assures me that the patch on the left forearm commenced several years ago with local pain, redness and swelling—and indeed now the affected skin at that site appears not only achromic, but also slightly shiny and atrophic. The other patches may really be vitiligo.

The blood-serum calcium is very low: two estimations in March, 1932, give 6·6 and 6·86 mgm. per cent. respectively. The patient has never had tetany or epilepsy, and neither Chvostek's, Trousseau's nor Erb's phenomenon can be obtained. Blood-serum cholesterol (March 14, 1932): 204 mgm. per cent. The Wassermann and Meinicke reactions (1927 and 1932) are negative, and the Pirquet reaction (March, 1932) is very weakly positive, as in normal adults. Brachial blood-pressure (March 8, 1932): 120/70 mm. Hg. By ordinary examination of the thoracic and abdominal viscera, eyes, blood-count and urine there is nothing abnormal. Urticaria factitia can easily be excited.

For some other details see the account given when I showed the case in 1927 (*Proc. Roy. Soc. Med.*, Clinical Section, 1927, xx, p. 46) as one of "persistent erythema with ischæmic circulation, in the left foot," but now, owing to similar involvement of the right foot, I am more inclined to the diagnosis (which I then thought could be excluded) of erythromélie (F. J. Pick, *Festschrift Kaposi*, 1900). Of this latter condition (whatever its exact nature may be) one of the few examples in England was shown at this Section by W. F. R. Castle (*Proc. Roy. Soc. Med.*, Dermat. Section, 1924-25, xviii, p. 26), and what I think was an equally definite example was shown, under a different heading, by Malcolm Morris and Ernest Dore much earlier at the same Section (*ibid.*, 1908, i, p. 89). The whole subject of erythromélie or acrodermatitis atrophicans chronica (Herxheimer and Hartmann) has been recently thoroughly discussed in a long critical review by M. Oppenheim in the second part of the eighth volume (1931) of Jadassohn's *Handbuch*, pp. 563-617.

In regard to the symptomatic use of the term "erythromelalgia" for the present case it must be admitted that the case is chiefly characterized by painful redness in the lower limbs, greatly aggravated by the dependent position, and that Maurice Lannois (1880) regarded erythromelalgia (the term introduced by Weir Mitchell in 1878) as a "vasomotor paralysis of extremities."

POSTSCRIPT (*June* 4, 1932).—Oscillometric index by Pachon's scale: In right leg (calf) 2·5; in left leg (calf) 0·5.

Section of Epidemiology and State Medicine.

President—M. GREENWOOD, F.R.C.P., F.R.S.

[*March* 16, 1932.]

Present Situation in France of Biological Prophylaxis and Treatment in certain Contagious Diseases, especially Whooping-cough and Measles.

ROBERT PIERRET, M.D. (Paris and La Bourboule).

EDITOR'S NOTE.—*Dr. Pierret's paper, as prepared, included sections on diphtheria and cerebrospinal meningitis. They are not here reproduced, as considerations of time prevented their being read, and the discussion was limited to measles and whooping-cough.*

FROM diverse circumstances, physicians and doctors in private practice in France often see more of infectious diseases, and have a closer concern with their prevention and treatment, than is the case in England, where they form a section of medical work much more closely and traditionally linked up with a specialized practice of public hygiene. There has, in consequence, developed in France a general professional outlook upon infectious diseases, whose nature is determined more often by the experience and teaching of recognized masters than by the evidence of records, reports, or statistics produced by public health officials. I propose to give some account of the current practice and teaching in France as regards "bio-prophylaxis" and "bio-therapy" of a few of the common infectious diseases, and to select whooping-cough and measles for the present paper.

WHOOPING-COUGH.

I should like, in the first place, to say that in whooping-cough, as in diphtheria, meningitis and measles, early diagnosis is of the greatest importance. The means at our disposal for this purpose were greatly assisted by Bordet and Gengou's discovery of a cocco-bacillus in 1900 and its cultivation by the same workers in 1906. I will not enumerate all the diagnostic methods which, from time to time, have been proposed, but will say at once that apart from the clinical signs (by which an experienced physician should in most cases be able to diagnose the disease before the onset of definite whooping) we have at present three chief diagnostic aids, namely (1) the isolation and culture of the organism, (2) the intradermal test, (3) a combined intradermal and therapeutic test, which I have employed with great satisfaction. To obtain successful results by the bacteriological method one must, as everyone knows, sow the material directly and without delay on a blood medium. In France this is usually done by making the patient cough into a Petri dish, but experience shows that this plan is not always reliable. A method which I employ as a routine gives a higher percentage of positive results and has the additional advantage that it can be used whether the patient is actually coughing at the time of examination or

not. It is therefore applicable particularly when a series of tests is being conducted in a school or other institution. It is based on the observation that patients with whooping-cough, in making an effort to stop the spasm of coughing at its onset, usually give the first few preliminary coughs with the mouth tightly closed. This means that they cough into the nasopharynx, which is therefore the site from which the specimen should be taken. For this purpose one can use for infants a straight swab introduced through the nostril, and for children aged over 3 years, a bent swab introduced upwards behind the soft palate.

The specimens are examined either directly or after culture. I employ, in addition to the cultural method, particularly when direct examination gives a negative result, a method which has both a diagnostic and a therapeutic value. In this procedure the vaccine of Nicolle and Blaizot—in which the organism killed by sodium fluoride is present to the amount of 250 million per c.c.—is employed. The dose for the diagnostic test is one drop injected intradermally. In addition to conducting this intradermal test it is my practice, in the case of every child suspected to be in the initial stage of whooping-cough, to inject the remainder of the contents of the 1-c.c. ampoule subcutaneously in another site. With this procedure I have obtained a positive intradermal reaction in 70% of cases which on clinical grounds I considered to be whooping-cough. In many cases the subcutaneous injection of the rest of the vaccine at that early stage arrests the cough immediately; in others a lessening or cessation of the cough is brought about by giving a daily injection of the vaccine for three days. In my opinion the positive intradermal reaction is an almost sure sign of incipient whooping-cough, and this diagnosis is usually confirmed by the results of the bacteriological examination which is always conducted at the same time.

You must forgive me for having described at some length this endeavour to establish a diagnostic method applicable to the earliest stages of the disease; my excuse is the importance to be attached to diagnosis at the earliest possible moment if the developed stage of the disease is to be effectively prevented by appropriate treatment, and also the undoubted saving of morbidity and mortality which can be obtained by any treatment which cuts short the attack or averts its serious sequelæ.

In France the bio-therapeutic agents at our disposal for the prevention of whooping-cough are: (*a*) the serum of convalescents; (*b*) the vaccine introduced by Nicolle.

(*a*) *Convalescent serum* (the only one used in France, because no therapeutic anti-whooping-cough serum is made in our country) is very little used. The results are practically the same as with measles convalescent serum, which is considered below. It will be sufficient here to remark that this serum has an action which is principally abortive, but is also relatively curative, and has a very definite therapeutic action if it is injected at the beginning of the disease or before the whooping stage.

(*b*) *Vaccinoprophylaxis.*—The first experiments in this direction were made by Nicolle and Conor, later by Bogert, Meyer, Lereboullet, Méry, Madsen and many others who all obtained satisfactory results. Spolverini claims 93% of successes, Luzzati 100% and Bogert 100%. Everyone will remember Madsen's success in the Faroe Islands, where all the inhabitants of some of the islands who had not been treated by prophylactic injections served to provide control observations on a large scale. In view of the results just cited it is not surprising that Nicolle's vaccine is being used to an increasingly large extent in France as a preventive.

Although various results showing the arrest of epidemics or the protection of contacts by a single injection of vaccine have been published, I consider, in common with other authors, that one injection is not enough and that the best method, where no premonitory signs are detected (such as slight fever and especially

catarrh) is to give three injections of 1 c.c.[1] (0·25 or 0·5 c.c. in the case of infants and children under three years of age) on alternate days. With this method one gets 90% of successes.

In cases in which there is even the smallest fear of the existence of whooping-cough it is best to give an injection every day, thus taking the first step in the work of aborting the disease; a true prophylaxis, in the strict sense of that term.

As to the composition of the vaccine, I should like to emphasize the necessity of using numerous strains and of employing doses equal to, or upwards of, 250 million organisms per c.c. Also I should point out that the organisms, if not still living, like those employed by Nicolle and Conor, should at least *not have been killed by heat*, which seems to reduce the therapeutic value of the vaccine. If a heated vaccine is used its concentration should be greater than 700 million—and even may be as great as 4,000 million—Bordet and Gengou bacilli per c.c.

Local reactions are altogether exceptional and when they occur are limited to slight local erythema and slight general rise in temperature, such as are observed sometimes with ordinary therapeutic injections.

To sum up on vaccinoprophylaxis: it can be said that anti-whooping-cough vaccine, if it could be administered to all contacts, would stifle epidemics in hospitals and villages, and would render whooping-cough one of the least important epidemic diseases instead of being, as at present, one of the most contagious and serious of all.

Before passing on to speak of vaccinotherapy, I should draw attention to the experience that children who fail to develop whooping-cough after having been prophylactically vaccinated either before the development of symptoms or during the catarrhal stage, do not gain a lasting immunity, and may contract undoubted whooping-cough a year or two later.

Vaccinotherapy.—It may be stated that at present, with the exception of the rare cases in which one makes use of convalescent serum, vaccinotherapy is the only specific biological therapeutic method in use.

The development of this method dates historically from the work of Nicolle and Conor in Tunis; it was the subject of a thesis by Pécourt at Paris, and of various interesting investigations by Benabu, Libert, Coste, Manucci, Rohmer, Brandenberger, Forest, Duverger, Bonnaimé, Leonardi, Nobécourt, Lereboullet and Lassablière. Nearly all these authors have used Nicolle and Blaizot's new vaccine, but a few used vaccines specially prepared by various technical methods.

It seems unnecessary to review all the work that has been done in this field. All that is called for on this occasion is a statement of the present position. I may first endeavour to state the general opinion with regard to the results obtained by this method, and then describe the technique to be used.

Vaccinotherapy gives the following results: Negative or partial results if used later than the third week of the disease, that is to say when a typical whoop has become established for more than ten days and when, to give a bacteriological and more accurate criterion, one can no longer demonstrate the presence of the Bordet-Gengou bacillus, or only do so with difficulty. This does not mean that the treatment is completely unsuccessful at this stage; it means that results are rapid but transitory. One must not forget, in fact, that after the third week the fixation reaction is positive and that the patient has already acquired all the immunity of which he is himself capable. It is not surprising therefore, that vaccinotherapy at this stage should be unsuccessful.

On the other hand, if vaccinotherapy is employed during the second and third weeks of the disease, that is, during the catarrhal stage and before the whoop becomes established, or when the Bordet-Gengou organism is still easily demonstrated, one obtains results which are much more clear-cut and satisfactory because one is

[1] 250 million organisms per c.c. of fluorized vaccine.

nearer the beginning of the disease. In the least promising cases the nature and duration of the coughing attacks are modified and the disease develops more mildly and is free from complications. Vomiting usually ceases after the third or fourth day of the treatment, sometimes even after the evening of the day on which the first injection is given.

In favourable cases one sometimes witnesses a real suppression of the disease which ends suddenly in from two to four days. In such cases, however, I would emphasize the importance of continuing the treatment as if the course of the disease had not been affected. If this is not done there is a risk of the reappearance of the whoop after a longer or shorter interval (i.e. five or six—or even, in one of our cases, fifteen—days) of apparent good health, and in such a recurrence the patient responds much less well, if at all, to vaccinotherapy.

One can therefore summarize the probable results of vaccinotherapy in whooping-cough as follows:—

On the general condition of the patient one can say that children treated remain in good health and that infants usually show a normal curve of growth and weight (Rohmer, Forest), especially if quinine is also administered.

Fever, which is unusual in any case in the absence of complications, also yields to vaccine treatment.

The greatest improvement is shown in the reduction of the number and violence of the spasms, and of the vomiting.

Finally, I have never seen any of the usual complications of whooping-cough in patients treated early.

I have had some very surprising results, particularly in an English lady of 72 who came to me from Monte Carlo on account of a curious spasmodic cough (she already had bradycardia from partial right-heart failure) with a view to undergoing special treatment; also in the case of a young French lady of 18 suffering from a clinically atypical form of whooping-cough, who was so ill and cachectic that a provisional diagnosis of galloping pulmonary phthisis had been made.

But I would again insist that if the vaccine is not sufficiently concentrated, if it is wrongly prepared (especially if it has been heated), and above all if the treatment has been delayed, the results will be inferior if not quite negative.

Vaccination technique in whooping-cough.—For prophylactic use the doses recommended by various authors vary from one to three injections of 1 c.c. of a suspension containing from 250 million to five or six thousand million organisms per c.c., the injections being given at intervals of from two to three days.

My own experience has led me to distinguish two types of cases:—

(*a*) That in which the presence of whooping-cough is not suspected and the problem is to protect a family or a group of children who have been in contact with a case of whooping-cough. In these circumstances I give three injections of 1 c.c. of fluorized vaccine containing 250 million organisms per c.c. at intervals of three days.

(*b*) That in which the presence of whooping-cough is suspected. In this case I give the same dose of the same vaccine every day for three days and a final injection two days later. If in such a case the diagnosis is established by an improvement in the symptoms or a return to normal of the leucocyte count (a good indication of whooping-cough in its early stages) or a positive bacteriological finding, then the suspicions were justified and the procedure to be followed should be the same as that of a definite commencing attack of whooping-cough. That is, one injects the vaccine, as above, every day for three days, giving the same dose each time, then one gives a dose every other day until six injections have been given, and finally from one to three additional injections (with the same dosage) are given, according to the results obtained with the previous injections. Two points remain to be mentioned. The first is that all these prophylactic and therapeutic doses should be reduced to

half or three-quarters in the case of infants. The second is that everyone in the community, including healthy adults, should be vaccinated. In one hospital it was found that the doctor himself was infecting his patients.

MEASLES.

I have kept measles to the last as it is the disease in which the use of convalescent serum has particularly to be considered, and is a subject, I believe, of special interest at the present time to the British Public Health Service.

Apart from the anxieties which measles brings into social and family life, this disease must be considered as being, in Europe, the most universally prevalent and the cause of a larger fatal mortality than any other infectious malady.

The great damage done by measles is evidenced both socially and economically, whilst its occurrences and sequels play a large part in infantile sickness and mortality. Here I propose to deal specially with its hospital aspect. The occurrence of measles in hospital has indeed two aspects—that of the welfare of the individual patient and that of the hospital itself. Both of these have their economical aspects, and economy is not to be neglected, at the present period in modern history, by any nation.

In communities of children, as in families, the secondary cases are by far the most numerous. Allowing no more than one or two secondary cases to each primary one, and reckoning that even a mild case of measles usually entails a stay of fourteen days in hospital, then, if we know the cost per child per day, we can easily calculate the economy which (taking full account of the expense of sero-prophylaxis) would still result from the prevention of secondary cases as far as this can be done. In so doing we must not lose sight of the further economy which would result from preventing the transmission of infection to new foci. I have not come across calculations of the expenditure entailed by the introduction of a case of measles into an institution, or even into a family, but they must be considerable. Perhaps in the near future serum prophylaxis will have so far advanced that neglect to apply it will place a serious stigma on the institution, or result in claims for damages on the doctor. What, even now, is the answer of the latter to the parents of the child who has died from measles contracted from his brother, if at the right stage prophylaxis had not even been suggested? The questions which may here arise of the relations of of the individual to the medical profession and also to public institutions or hospitals, are worth reflection.

At the outset it should be said that in present knowledge convalescent serum has no therapeutic value. In a conversation which Sir George Buchanan and I had recently with my colleague Reilly in Paris, the latter considered this accounted for by the convalescent serum not possessing a sufficient richness in antibodies. This explanation is possible and even probable. One must remember that in the case of the usual antitoxic and antibacterial sera it is not the transmission of the disease itself which produces the curative serum—the necessary richness in antibodies results from the artificial introduction of toxins on successive occasions.

It would be interesting to know whether the serum of the patient who has recovered and is convalescent is more or less rich in antibodies than the serum of a person who, little by little, had been experimentally accustomed to resist the infection. It would in this respect be interesting to inquire about the effect of giving to persons, suffering from poisoning, serum obtained from other persons who had recovered from or were habituated to the same poison. Apart from snake venom, I do not know of any experiments in this direction, for example, with morphine or with alcohol. One can hardly expect to have the opportunity of treating persons who have taken an overdose of opium by injecting the serum of a convalescent morphinomaniac, still less be able to give relief to a friend who has celebrated a family anniversary too freely by an inoculation of serum obtained from an old chronic alcoholic!

Nevertheless, experiments might be devised in other ways to show whether in man an antitoxic quality is best produced after heavy intoxications or follows repeated slight intoxications. It is in any case well established that the sera of nurses in a measles ward are more protective than the sera of ordinary persons who have had measles long before, but have not been exposed to re-infection. This does suggest that the absence of therapeutic—though not of prophylactic—activity in convalescent serum may well be the result of its containing too small a concentration of antibodies.

Another consideration may be referred to. Theoretically, the fact that a measles patient is convalescent does not necessarily mean that he is entirely free, either from the virus or from the toxins elaborated by the virus. What is certain, however, is that in the blood of the convalescent the potency of the virus-toxin complex is inferior to that of the antibodies produced by the body. It was an objection of this nature that led Professor Teissier originally to point out that the injection of convalescent serum might involve the danger of infection as well as the advantage of immunization.

The faculty of responding to immunization, as everyone must admit, varies greatly with the individual and so, if we consider convalescent serum in terms only of its antigenic-antibody neutral state, we must consider the serum as having value only in a certain concentration. Once this concentration has been disturbed by the subcutaneous injection into another individual, the virus may again take the upper hand.

These technical considerations, though worth mentioning, are not based on any conclusive experimentation. Would it not in any case be useful to obtain data by differential experiments made by injection of serum which has been collected at different periods during the first seven days after defervescence? Failure to protect has been attributed by Teissier specially to the use of sera which are too old. But failure may also be obtained by the use of sera collected too soon after defervescence. These failures might prove to be followed by the occurrence of definite attacks of measles, so that in these cases the injection of serum would not only have failed to prevent the appearance of measles, but have actually caused the disease to have occurred. Such questions as these of course arise only with the use of convalescent serum and not in the case of the serum of ordinary adults attacked by measles long before.

Other objections may be made to convalescent serum. In the first place, the short duration of the immunity. The protection hardly lasts more than four or five weeks, so that if it were to be relied upon to protect a subject remaining in an endemic centre, for example in a large town, he would need to be perpetually re-inoculated.

Another objection is that the collection of serum is an uncertain matter. There is not enough of it at the beginning of seasonal epidemics, and it becomes abundant at the time one needs it least. It may be said that this is only a matter of storage and the serum can be kept in the refrigerator, but preservation seems to have uncertain results, and in any case should presuppose a faultless refrigerating plant. All conclusions drawn by authors about the failure of sera on keeping are fallacious if this primary condition of permanent and continuous cold has not been fulfilled.

In this connection the possible existence of a difference in the protective value of sera, according to whether they have been collected from cases at the beginning or at the end of an epidemic, deserves noting. In determining this matter also, we meet with the difficulty that our knowledge of the potency of the serum is only theoretical and limited. If serum in fact loses its effect on keeping, may not the explanation be simply that the margin of safety against its loss of sufficient activity is a very small one, seeing that the initial concentration itself was small?

Besides such theoretical doubts, for what they are worth, one should mention two practical difficulties: (1) in obtaining sufficient quantities of serum, and (2) in finding voluntary donors, either among children (though this is relatively more easy) or among adults. It seems probable that in practice we shall habitually have to seek our donors among the personnel of hospitals, doctors, students and nurses in measles wards.

I have dealt perhaps too long on objections and difficulties, some of them rather theoretical than practical. I now come to the ordinary application of this prophylaxis in France, borrowing the essential particulars from the publications of Debré, Joannon, Reilly, Teissier, Nobécourt, Paraf, Méry, Gastinel, Godlewski and Harvier, who popularized in France the discovery of Nicolle and Conseil dating from 1916. Among foreigners I may specially refer to Degwitz of Munich, who did a great deal of work on the question when it first arose.

There arise from all this study considerations of periods of time in connection with (*a*) a donor of the serum, (*b*) the person to be immunized, whether incubating measles or not.

The donor of serum should only be utilized after seven full days have elapsed since the final defervescence. It is at this time that the convalescent serum is richest in antibodies; the immunizing value subsequently decreases each day and becomes feeble about the third week. There is another consideration in favour of not collecting the serum until seven days have elapsed, namely, the possibility of the incubation of another disease in the intended donor: a point specially important when collecting serum in the hospital.

If the person to be immunized is not in the incubation stage of measles, it is assumed that the immunity will not last more than a month, i.e., about the time which it takes to eliminate average doses of foreign sera injected subcutaneously.

If the person is in the incubation period, the only chance of obtaining complete immunization with proper dosage is during the six days following his infection. After that time one does not obtain complete immunity but "only" an attenuation of the measles, occasional set-backs being allowed for. This word "only" is not to be used in any disparaging sense, for in fact the real objective for the individual should rather be his protection against successive epidemics than against the one to which he is exposed at the time. Here indeed we may agree with the majority of authors in considering that, except for infants, it is of greater value that a mild attack of measles should be definitely produced, seeing that it is only by an attack of the disease itself that complete immunity for the future can be secured.

There are many circumstances which make the exact and regular application of this system impossible, more particularly the uncertainty of the exact date of first exposure to infection. This is the more important since it is only during the seventh, eighth and ninth days of incubation that an attenuation of measles can be produced by the inoculation of convalescent serum.

It might be supposed that when the practical means of measuring the immunizing activity of a given serum has been found, one might hopefully proceed by following a mathematical formula which would have as its principal factors: the time, T, in hours which have elapsed since the moment of infection; C, the concentration of the serum in immune bodies; P, the weight of the person to be immunized; K, the indispensable constant in every mathematical formula applied to biology, calculated according to blood-groups, the urea content of the convalescent serum (a matter with which no one has yet dealt) corrected by the inevitable Δ, and, finally, a coefficient Hh representing the degree of hereditary affinity, if any, between the donor and the receiver. I leave to others this formula and proof that sero-attenuation could be attained by it.

Even now, however, we are in a position to maintain that seroprophylaxis by means of the convalescent serum (which we owe to Nicolle and Conseil), extended to

the inclusion of the serum of adults who have formerly had measles, is one of the most valuable acquirements of modern bioprophylaxis.

To come now to describe the practice as it is usually taught and accepted. The collection of the serum includes first the *selection of the donor*. The donor should be a person over ten years of age and preferably not under eight.[1] There must be no doubt that he has just had measles, he should also be healthy, not only being free from syphilis (we need not exaggerate the danger of syphilis, especially if the blood is kept in the refrigerator), but also from tuberculosis and malaria; the defervescence should be complete and no complications should exist in the convalescent of whom the general condition should be good.

Pregnant women and persons who have had a recurrence of measles should be excluded (Debré, Joannon), as a recurrence shows incapacity for immunization.

Every possible precaution should of course be taken to eliminate the hazard of an incubation stage of some other infectious disease such as mumps, typhoid fever, rubella and, especially, scarlet fever.

Time of collection.—This should be on the 7th to the 9th day after defervescence; after the 12th day the efficacy becomes more and more uncertain.

Apparatus.—Many kinds of apparatus can be used, on the lines of those employed in bleeding for bacteriological purposes; it is well—but not essential—to prevent coagulation by paraffining anything which comes in contact with the blood, except the coagulation vessel.

An average of 50—60 c.c. is taken from a child and 80—100 c.c. or more from an adult.

Preparation of the serum.—The coagulation takes place at the ordinary temperature (I think the optimum temperatures should be determined). The serum is kept for at least 4 days in the refrigerator before use, in order to kill any possible treponemata. Each tube of serum is controlled by a bacteriological culture test and a Wassermann test.

The sera are then mixed, 6 to 8 together (noting the serial number of each serum) in order to obtain for use a serum with as constant a potency as possible. A fresh culture test is made of the mixture; it is then divided into ampoules containing 3 or 5 c.cm.; some of the ampoules are again bacteriologically tested. They are kept in the refrigerator. Thus kept, the serum may, according to Debré and Joannon, remain active for several months. According to Teissier and Reilly (who, unlike the former, work chiefly with the serum of adults) they suffer a fairly rapid loss of activity on keeping.

The physician thus equipped should give the benefit of this immunization by preference first to infants, next to children under 2 or 3 years of age. In practice, preference is also usually given to hospital cases, and then to delicate children in families and schools, sickly children, convalescents from other diseases, and children undergoing surgical treatment in children's hospitals, and so forth.

When this convalescent serum is available, one ought not to experience any epidemics of measles in hospitals or hospital wards. If a case of measles occurs in a hospital ward, all the other children who are not definitely known to have had measles should be immunized. The prevention of an epidemic in these circumstances is perhaps the greatest benefit which we obtain from seroprophylaxis. Even newborn children of mothers who have active measles may be inoculated.

It is undesirable intentionally to produce sero-attenuation of measles (as opposed to immunization) in children under 3 years of age.

[1] In the Hôpital des Enfants Malades, in Paris, blood is not infrequently taken from children not more than 3 years of age.

Doses to be inoculated.—Young infants should have an injection of at least 4 c.c., children from 3 to 10 years of age 6 to 7 c.c. and older children 9 to 10 c.c. These are doses higher by from 1 to 4 c.c. than the "classic" doses. The danger lies not in injecting too much but in injecting too little. It must be admitted that a principal cause of small dosage is that the Institutes which supply the serum give it out very sparingly.

Several authors have, like myself, observed the attenuation of measles through insufficiently strong injections during the first six days of incubation; this shows us a second method, which is however more problematical, of obtaining attenuated measles at will.

The usual injections are subcutaneous, unless more than eight days have passed since the contact which resulted in infection, in which case it may be intramuscular. No result is obtained from their being given after the tenth day of infection.

I touch here only briefly on the use of serum of adults who have previously had measles; this also possesses an immunizing action but it appears to be much less, and especially much less regular, than that of the convalescent. In any case a considerably greater dosage must be given.

One may also mention the possibility of using citrated whole blood, but in that case very large doses indeed would be required. We have to remember that the serum only represents 40 to 50% of the blood drawn and that therefore whole blood is only half as active. If we are dealing with a donor who has formerly had measles, and using whole blood, we may empirically multiply the dose by four or five in order to hope for results equivalent to those of convalescent serum. If the case is very urgent, and if the family doctor knows the parents' antecedents, citrated whole blood may be collected from them (particularly the mother's blood) and used without previous laboratory examination. I would certainly advise those who have no experience of attenuated measles to use convalescent serum.

I may note here that, without previous experience, doctors confronted with cases of attenuated measles usually think that they have discovered a new disease because of its different characteristics, or that they are dealing with a case of rubella.

It may be that in England there are special homes for delicate, backward or pre-tuberculous children in which epidemics of measles frequently occur, and I would venture to urge the health services concerned to carry out some trials in these institutions, if they have not already done so. I feel sure that they will become fervent enthusiasts in favour of the method, in spite of difficulties of organization, some failures, and a few reactions which may result from its use.

Failures, accidents, reactions.—In point of fact, like every biological method, including Jennerian vaccination, the seroprophylaxis of Nicolle and Conseil is not a mathematically exact method.

The failures are very few in number if large doses are injected (large even if recently prepared convalescent serum is used) and if the injection is not given too late, but they may be twice as many if the serum is more than two months old, especially so if it is adult serum[1]. Failures which cannot be attributed to an inadequate technique do not exceed 2 to 5% of cases.

Accidents due to bacteriological pollution of the serum need not be taken into account as an argument against the method. Records of a few such cases have been published in France. To guard against them some institutions heat the serum for one hour at 56° on two consecutive days or add antiseptics. In Paris we do not adopt either course, for fear of lessening the anti-morbillic activity of the serum.

Toxic accidents, comparable to serum disease, do not occur. Except in one case the erythemas observed have been recognized to be only attenuated measles rashes.

[1] If the blood or serum is that of a patient who has in the past had measles there is all the more reason for giving double or even quadruple doses. The dose should also be doubled in the case of children who are already ill.

On the other hand, general reactions are sometimes met with, perhaps in 3% or 4% of cases, with temperature rarely exceeding 100·2°F. to 100·4°F., loss of appetite, insomnia and restlessness. Locally there is a red and hot œdematous swelling, which is painful and comparable to Arthus's phenomenon. However severe these reactions may seem, all the symptoms clear up in one or two days without complications. They are of the anaphylactic type which have been met with in adults after injections of normal human serum, and have no connection with measles. So far as I am aware, no cases have been published in France in which a serum disease with arthralgia, fever, erythema, pruritis, etc., occurred, nor have any cases been recorded of shock with rigor or collapse, etc.

These rare incidents (Cros-Decam's thesis) are no more a contra-indication of the use of the method than is the fever, etc., which we meet with far oftener in our doyen of inoculations—Jennerian vaccination.

Discussion.—Dr. J. A. H. BRINCKER: The subjects just presented by Dr. Pierret are particularly opportune, as we are just now experiencing one of the usual severe outbreaks of measles which afflict London every two years, while the prevalence of whooping-cough has been trying our patience for some years now. More lives of young children are lost annually from this disease than from any other of the infections to which such young children are subject. I was interested to hear that Dr. Pierret has had such marked success with the treatment of whooping-cough by vaccines. At the suggestion of the Ministry of Health a year ago we in London tried the value of Bordet vaccine, and the results of the trial carried out in two of our fever hospitals and in two children's hospitals were most disappointing, as the vaccine used appeared to have no effect on the outstanding symptoms of the disease, such as coughing and vomiting, or in preventing complications and death. The results of the experiment in the two fever hospitals are recorded in two papers by Dr. Nancy Howell and A. R. Thompson in the Medical Supplement of the London County Council's Medical Officer of Health's Report for 1930. The disappointing results obtained in these cases will, no doubt, be attributed to the treatment being started too late in the disease, as cases are usually admitted when the disease has become fully established. It may be added, however, that when the vaccine was tried on contacts of cases it did not succeed in preventing an attack of the disease. As far as I am aware, serum from recovered cases has not been tried in this country, but I hope we shall have an opportunity soon to put it to a practical test.

The treatment of measles by serum, however, has been more satisfactory in London. This year the London County Council has been trying an experiment on the prophylactic value of adult human serum. As far as can be judged, the results obtained have been very promising, but the experiment is still in progress. As convalescent serum is very difficult to obtain in quantity, and as it does not retain its potency when stored for any length of time, the use of fresh adult serum, particularly in the earlier stages of an epidemic, may prove of very great value in the prophylaxis of the disease. We are testing this serum in children's wards of the Council's hospitals, institutions and residential schools; the object in view is to protect delicate children accidentally exposed to measles, and to prevent the development of secondary cases in a ward or school, and so avoid the necessity of applying quarantine regulations to them.

Outbreaks of measles have always been of special interest in London, as they seriously affect school attendance. As soon as medical inspection of schools was instituted, it became apparent how such outbreaks interfered with the school curriculum, and also seriously affected the physical welfare of the child. All sorts of experiments were tried to curb the spread of the disease in schools, as, for instance, by school closure, or complete or partial exclusion of susceptible children for varying periods, but it was soon clear that the disease could not be controlled by these means. They were therefore abandoned in favour of means for the early detection of cases and of providing careful nursing. The scheme which we now enforce in schools is to detect children sickening with measles, to admit to hospital those coming from the poorer and more congested homes, and to provide satisfactory nursing for the remainder; our aim in both cases is to prevent the development of complications, and so reduce the chances of the child dying or being seriously injured.

At a rough estimate about 50,000 London children suffer from measles during each epidemic; it is therefore evident that prophylaxis by the use of serum, apart from its use in

institutions, schools and hospitals, is quite out of the question. That the measures and precautions taken have a salutary effect is apparent from the fact that measles mortality has been reduced during the last ten years.

Sir ALMROTH WRIGHT said that the evidence on these subjects had not been derived from exact scientific study or experiment. The impressions and conclusions firmly held by a clinician with one kind of experience and using one kind of treatment and prophylactic were not necessarily to be preferred to contrary conclusions and impressions by another clinician with different opportunities and using other materials and technique. No one, however, would wish to depreciate the value of such clinical work; often it was the only way in which any progress could be made in these matters. He thought Dr. Pierret assumed too readily that the blood was richest in antibodies directly after the disease. In typhoid the patient scraped through with no balance of antibodies to spare. In whooping-cough, in which the organism was known, it should be possible to assess the value of vaccines accurately by scientific methods, not merely by clinical impressions. The vaccine used in this country had certainly been exposed to heat; he was not himself convinced that other methods of treating the vaccine were more satisfactory.

Dr. W. GUNN said that bio-prophylaxis of measles in France and England differed in two important respects. In the first place, in France, the supervision of measles patients and control of measles epidemics appeared to have remained in the hands of the general practitioner, while in this country the public health services and ancillary agencies had organized schemes for the treatment and after-care of measles cases, especially in over-crowded areas where such were needed most. In the second place, it was noteworthy that the dose of serum employed to prevent or modify an attack of measles was much smaller in France than had been found necessary in this country. He, Dr. Gunn, thought that there must be a direct causal relation between the dose and the circumstances under which exposure to infection and the consequent need for sero-prophylaxis were scrutinized. A distinction should be made between possible contact and probable contact: the indiscriminate injection of serum when the likelihood of effective exposure was remote was to be deprecated, as giving a false sense of security and of serum potency. It was easy to show a high percentage of successes under such conditions, but the inevitable failure would turn up, and, from the administrative viewpoint one failure in a hospital ward was almost as bad as half a dozen. Investigations, as carefully controlled as experiments on human subjects permitted, showed that a minimum dose of 5 c.c. of serum was necessary; from the age of 3 years onwards the dose was reckoned in cubic centimetres by multiplying the age in years by two. Provided that the serum was given during the first five days after exposure and that the injections were made intramuscularly, no failures ensued. Strictly speaking, the dosage should be adjusted to the body-weight, not to the age, for wide variations in weight are met among children of the same age, but the doses mentioned were found sufficient to provide the margin of safety needed to correct this error. Dr. Pierret had shown a tendency to regard as successes all inoculations which appeared to modify severity of attack. To his, the speaker's mind, an injection was recorded as a success only when the aim desired, protection or attenuation, was attained. An attenuated attack was almost as infectious as an ordinary attack and gave rise to infections of normal severity. The inoculation period was not appreciably lengthened when an attenuated attack followed, although some writers had recorded instances of this.

Owing to the difficulty of securing an adequate and constant supply of convalescent serum, the London County Council had organized, this year, a comprehensive scheme for the collection of adult blood from voluntary donors in their service. Up to the present they had collected and prepared an amount of serum equal to 2,000 doses, of which approximately three-quarters had already been administered. In doses exactly double that of convalescent serum, the product had been found hardly less efficient than the former, but it was necessary to inject during the first three days to secure as constant results in prevention, although for attenuation there was little to choose between them. Arrangements were in hand to concentrate the serum to approximately one-third of its bulk, and, should enough supplies be available at the end of the present epidemic, it was hoped to store it in powder form in readiness for the next epidemic two years hence.

Dr. DAVID NABARRO said that since the year 1928, when he was requested by the Ministry of Health to endeavour to obtain a supply of measles serum and to use it when the opportunity arose, he had, with the co-operation of Dr. Massingham, of the London Fever Hospital, been

able to obtain sufficient serum for the treatment of about 1,000 children. On the whole the results had been extremely favourable, and until last year the successes had been over 98%. During the recent epidemic, however, there had been a certain number of failures to ensure complete protection, and probably these failures were attributable to the fact that the serum had been stored for a considerable time, perhaps as long as nine or twelve months. As a result, the dose of serum now being employed was about 50% greater than it had been previously.

With regard to the collection and preparation of the serum, he, Dr. Nabarro, had always obtained the blood from adults, because he thought it inadvisable to bleed children who were recently convalescent from measles as this might unnecessarily retard their convalescence, and also because there was always a possibility that a latent tuberculosis might have been stirred up by the attack of measles itself.

After the serum was obtained, it was filtered through a Seitz filter and 0·5% phenol added to it. Apparently neither of these procedures was adopted in Dr. Pierret's laboratory, and he wondered whether in Dr. Pierret's opinion there was any objection to using them. He agreed with Dr. Gunn that owing to the size of the injection, especially in small children, concentration of the serum would be desirable, because he had had a few cases of infants under the age of one year who had experienced rather severe reactions (rise of temperature to 101° or 102° and severe malaise) following upon an injection of the serum.

He had recently had an interesting experience at Great Ormond Street Hospital in two wards, in both of which a case of measles had occurred. In the one ward all the children were given a dose of serum with the result that there was not a second case of measles. In the other ward, in which the physician in charge was opposed to the practice, the children were not injected, and eight further cases of measles occurred amongst them and one nurse contracted the disease.

He would like to emphasize one point, namely that it was unwise to omit injecting children who were stated to have had a previous attack of measles. On several occasions when he had been told this and had consequently not given an injection, the child developed measles.

There was no doubt that convalescent measles serum was a very potent means of preventing measles entirely or, perhaps better from the patient's point of view, producing an attenuated attack of the disease, and he hoped that Dr. Pierret's address would stimulate the authorities in this country to further action in this matter.

Dr. J. D. ROLLESTON emphasized the epidemiological importance of whooping-cough in adults, which often escaped recognition, and, when it attacked nurses, might account for otherwise inexplicable outbreaks of the disease in children's wards. He agreed with Dr. Brincker's remarks on the disappointing effect of the vaccine treatment of the disease.

With regard to the use of adult human serum in the prophylaxis of measles, he could confirm from personal observation what his colleague, Dr. Gunn, had said. When the serum did not prevent the disease entirely, the attack was usually so mild that he had now no hesitation in leaving such a case in the ward where it occurred when the other patients had been protected by similar injections. The mitigated attack was very similar to that following injection of convalescent serum which had failed to confer complete immunity. Dr. Lichtenstein,[1] Medical Superintendent of the Stockholm Fever Hospital, had recently reported that convalescent serum for the prophylaxis of measles and poliomyelitis and treatment of scarlet fever could be preserved in a dry state and still prove efficient after the lapse of two years. With regard to the prophylatic use of convalescent serum in other diseases, an account had recently been published by Pauzat and Lévy[2] of the encouraging results obtained in the prophylaxis of serum-sickness following injection of antitetanic serum.

Captain S. R. DOUGLAS said that in many virus diseases immunity following an attack was extraordinarily solid and permanent, for instance in the case of yellow fever; the serum had moreover been found to have protective properties many years after an attack of the disease.

It had been found by experiment in the case of dog distemper that convalescent serum—or, better, the serum of a hyper-immunized dog—had great protective power. This fact had

1 *Med. Klin.*, 1932, xxviii, 299.
2 *Gaz. hebd. Sc. Méd. de Bordeaux*, 1932, liii, 71.

been put to practical use in this disease in the following ways: (1) by inoculating immune serum on one side of the animal and many infective doses of virus on the other side, a solid immunity was produced; (2) in the early stages of the disease a dose of serum, preferably concentrated, aborted the attack, and even when the disease was fully developed larger doses of concentrated serum often led to rapid recovery.

The difficulty of investigating measles was that it was at present impossible to reproduce the disease in a satisfactory manner in the lower animals. Monkeys occasionally were infected, but the disease could not be passaged in series. If only one could discover an easily available and sufficiently large animal which could be infected regularly with measles it would be a comparatively simple matter to work out the best method of preparing a hyper-immune serum.

Sir GEORGE BUCHANAN said that progress would be impossible if they had always to wait for exact scientific and properly controlled trials before using particular vaccines or serums. Since last year the assessment of the value and necessary dosage of different anti-meningococcus serums had become specially important because of the increase in cerebrospinal fever. According to the scheme adopted at the Ministry of Health, records on these matters were being obtained for practically every notified case treated with serum. Their detailed analysis, however, presented great difficulties owing to the many variables, and it might well prove that they would obtain better indications by trusting to the impressions of competent clinicians, particularly in matters where they coincided.

As to the therapeutic value of vaccines in whooping-cough, he presumed that Dr. Pierret would say that vaccine treatment had been rejected in England on evidence of the wrong kind, the unsatisfactory results having been in cases treated at too late a stage of the disease, and that bacteriological diagnosis was not used as it should be on his contention. But the right sort of evidence seemed by no means easy to obtain; many slight and atypical cases of whooping-cough occur normally, which would probably be credited to the vaccine in vaccinated cases.

A graph of measles deaths [exhibited] showed that the reduction of measles mortality in London during the last ten years, which Dr. Brincker was inclined to ascribe to special measures, was equally characteristic of the whole country. The efforts now being made to extend the use of convalescent and adult serum were fully justified for the prevention of hospital outbreaks, and still more for the benefit of the individual, who was thus given an attenuated attack.

Dr. E. W. GOODALL said it was clear from the fatality curves exhibited by Dr. Pierret that the severity of the common infectious diseases was different in Paris from what it was in England and Wales. Whooping-cough appeared to be more severe here than there. This difference of severity, as indicated by the fatality, must be borne in mind when effects of treatment were compared. Measles was a disease which varied greatly in its fatality from year to year, as was shown many years ago by the notification figures for twenty years in Aberdeen, where the fatality varied in different years from 0 to 25 per cent.

The discussion had turned chiefly on the specific treatment and prophylaxis of measles. In this country little seemed to have been done in those directions in respect of whooping-cough. Yet that disease was now, and had been for some years, the most fatal of the common infectious diseases. It usually accounted for more deaths in children under one year of age than any of the acute infections except infantile diarrhœa, and in many years its death-rate was higher than those of measles, diphtheria and scarlet fever. As also it was a disease which led to many cases of permanent disability, especially of the lungs and chest, more effort should be made to reduce its prevalence than was apparently being made at present. His (the speaker's) experience, as the result of post-mortem examinations, led him to the conclusion that an attack of whooping-cough was much more likely than was one of measles to rouse into activity a latent tuberculous focus.

Dr. Pierret had laid some stress on the necessity for making an early clinical diagnosis in whooping-cough. But that was by no means always easy. It was not infrequent for the catarrhal stage of the disease to be entirely absent; there was no catarrh, or cough, or pyrexia, and the first sign of the attack was the whoop. By that time the toxin had got a firm hold of the patient, just as it had when paralysis supervened in diphtheria and the spasms in tetanus.

The therapeutic treatment of infectious diseases in the hospitals of the London County Council was handicapped by the fact that the patients were not sent to hospital till a definite

diagnosis had been made, and this was not done until the whoop appeared in whooping-cough and the rash in measles, so that there was much delay before the appropriate treatment could be begun.

From the evidence brought forward that evening by Dr. Pierret and other speakers, he, Dr. Goodall, was of opinion that the prevention of measles by the measures described had been established, but he was not so certain of the therapeutic results.

The PRESIDENT said that it only remained for him to express, on behalf of the Section, their unanimous and hearty thanks to Dr. Pierret. There were not, he thought, any nettles in the bouquets showered by members. Sir Almroth Wright, like himself, took a sentimental interest in logical reasoning and no doubt it would, from that point of view, be desirable that Dr. Gunn should explain in a little more detail just what he meant by a strict logical " control." But he (the President) agreed with Sir Almroth that practically important discoveries were frequently made by methods which no strict logician could countenance. It certainly could be argued that credulous and illogical ages of the world, such as the present, reached more practically important results than those achieved by such strictly logical reasoners as, for instance, St. Thomas Aquinas, who lived in an age when purely intellectual methods enjoyed a much higher prestige than now. The meeting would join with him in regretting that the length of this discussion and the lateness of the hour prevented him from calling on Dr. Pierret for reply.

Section of Odontology.

President—Mr. E. B. Dowsett, D.S.O., L.R.C.P., M.R.C.S., L.D.S.E.

[*April* 25, 1932.]

DISCUSSION ON MOUTH-BREATHING AND NASAL OBSTRUCTION.

Opening paper by W. Warwick James, F.R.C.S., and Somerville Hastings, M.S.

For many years we have jointly examined patients suffering from conditions generally believed to be associated with mouth-breathing and nasal obstruction. The observations recorded in this paper are based almost entirely upon our clinical experience.

The constant use of the nose for respiration.—In mammals, birds and reptiles, the nose is the portal for entry of air in the respiratory system, whilst the mouth, the portal to the digestive system, may be used to supplement the respiratory function of the nose, under certain conditions. We wish to emphasize the fact that in man, nose-breathing is normal in all races, although the use of the mouth to supplement normal respiration occurs during severe muscular exertion and also in special acts such as yawning, coughing, sneezing and crying. Under conditions which demand rapid filling of the lungs with air, inspiration through the mouth is more effective than through the nose, as can be readily demonstrated. When respiration takes place with the mouth open, the position of the soft palate and tongue varies, according to whether the nose or mouth is mainly used. If the base of the tongue is raised and the soft palate depressed, the air enters through the nose, but if the tongue is depressed and the soft palate raised, the air enters through the mouth. Our observations have led us to believe that, except in a few rare pathological conditions, the nose is always used for respiration although at times supplemented by the mouth.

The powerful urge to breathe through the nose is present in all individuals. It is most marked at birth and would appear to diminish in old age.

We have made use of a strip of thin paper about one-eighth of an inch wide and two or three inches long, to determine the character of the breathing, one end of the strip being held by the hand and the other placed close to each nostril and before the mouth, alternately and repeatedly. In children we have found it useful to distract the attention by pretending to test the eyesight and asking the child to follow the same or a second strip of paper with his eyes while the test is being carried out.

We have examined fifty-three infants, aged from 1 to 14 days, while asleep, in the maternity wards of the Middlesex Hospital. In every case breathing took place exclusively through the nose. One of these children was sucking two fingers and another the thumb. Several had their lips apart. In some, but not all, of these last, the oval or triangular space between the lips was plugged by the tip of the tongue. All these babies had well-developed alæ nasi muscles. The mandible and lower part of the

face appeared to be relatively small, the chin receding and the lower lip well behind the upper. We tried the effect of pinching the nose between the finger and thumb; for about 20 seconds the babies slept on peacefully, then they began to struggle and to cry. The mouth was not opened till the moment of crying, except in the case of one child who was sleeping with the lips apart, and in his case the mouth was further opened and an inspiration taken before crying commenced. How great the urge for nose-breathing is in the very young is shown by a case of congenital obstruction of the post-nasal orifices recorded by C. W. Richardson. He was called to a new-born infant and tells how it would be at rest for a moment with lips closed and cheeks slightly indrawn and then struggle for air with its face suffused. Almost immediately it would begin to cry and the dyspnœa being thus relieved, it would settle down quietly until the cycle commenced again. Only if the lower lip was depressed would the child breathe through its mouth without crying. By relays of assistants the lips were kept apart and at the end of its second week of life the child had learned to maintain mouth-breathing. Richardson suggests that some children with congenital obstruction of both posterior nasal orifices never succeed in breathing at all and are still-born.

The absence of mouth-breathing where anticipated.—It surprised us greatly to discover how very few of those children who habitually have their mouths open really make use of them for respiration under ordinary circumatances.

We tested fifty-four children who had the mouth open by day. They comprised those who came to the out-patient department before operation for tonsils and adenoids, and those admitted to the children's ward for other conditions. In ten the mouth was used for breathing by day; seven used the mouth as accessory to the nose; three used the mouth only; but at night three of the ten used the nose only. The remaining forty-four had the mouth open by day but breathed only through the nose. Of these, thirty were tested at night when asleep; two used the mouth only; four both the nose and mouth; twenty-four used the nose alone, and of these five had the mouth shut.

Several adults who had their mouths open habitually were tested by day, but in each case the nose only was used for respiration. In old age, especially when the teeth are lost, the mouth is often open at night. Negus has shown that in many animals, especially those with a highly developed olfactory sense, the epiglottis is long and is in contact with the soft palate so as effectively to shut off the airway from the mouth, but at no stage in development is this the case in man. Therefore, as there is no difficulty in mouth-breathing for mechanical reasons, the urge to nasal respiration must be regarded as physiological. Darwin has pointed out that "the adult man can in fact draw a full deep inspiration much more easily through the widely open mouth than through the nostrils." And yet not only man, but—apparently without exception—all mammals, birds, and reptiles, breathe through the nose in quiet respiration and in sleep. Possibly the continuous exercise of the sense of smell may be of value to the organism. It would seem more likely however, that mouth-breathing animals have not survived, because of the value of the nose in cleansing the air and thus protecting the individual from throat and lung affections. Possibly in the past, variations of species acquiring the easier habit of mouth-breathing may have been wiped out by intercurrent disease.

The normal nose and nasopharynx.—The mucous membrane of the normal nose contains erectile tissue which is usually present in largest amount on the inner surface of the inferior turbinated bones. Catarrhal infections or a warm, moist atmosphere may produce swelling of this tissue. The septum nasi lies in the middle line and is not deviated to either side. There is often some thickening at the junction of the vomer and perpendicular plate of the ethmoid, opposite the anterior ends of the middle turbinates. The upper regions of the nose vary anatomically a good deal in normal subjects. Keith is of opinion that considerable changes have

taken place in the normal nose and face since the Roman period. Civilized man of to-day possesses a smaller face with less defined features than the more primitive type. It would seem probable that diminished use of the muscles of mastication is mainly responsible for this.

To what extent, if any, adenoid tissue is present in the nasopharynx of the normal child is uncertain. A few years ago one of us had occasion to examine with the mirror the nasopharynx of each of some five or six hundred London schoolboys of 12 to 16 years of age. An appreciable amount of adenoid tissue was present in the nasopharynx of a large percentage, and this was true of many of those who had had their adenoids removed by operation. The percentage of children in whom definite adenoids are present is given differently by different authorities and varies between 62% and 10·2%. Burger, by compiling the statistics of many observers, concludes that adenoids are present in some 29·8% of children. We must not forget, however, that there is much diversity of opinion as to the exact stage at which adenoid tissue in the nasopharynx should be regarded as pathological.

Normal mouth.—The normal mouth must be fully understood in order to comprehend changes which can be regarded as pathological. Evolution of the jaws implies a changing normal. These changes are gradual, but at any one period it should be possible to conceive an ideal normal, which should be most favourable to the individual both for function and for prevention of disease. In infants the mouth is remarkably unformed as compared with that of the adult. Shortly after birth all individuals possess a resemblance in the arrangements of the lips and in the position of the mandible, which is placed rather far back relative to the whole face. The lips are somewhat everted, the lower being definitely behind the upper; together they have a triangular appearance. The roof of the mouth is flat, with little more than an indication of the alveolar ridges. The mandible is small and extremely mobile. The act of sucking itself, whether food be taken or not, means that the tongue must come into contact with the palate, the soft palate is depressed, the lips and cheeks are drawn inwards. This action must play an important part in development of all the structures concerned. The potentialities of growth exist, but the moulding of the parts is largely dependent upon mechanical factors which are due to the action of the muscles of the tongue, of mastication and of facial expression.

Temporary dentition.—The eruption of the temporary teeth provides a further mechanical stress upon the bones of the face and skull by the pressure exerted and the necessary resistance when the teeth are occluded. The tension of the muscles through their attachments to the bones of the skull, face, and mandible, becomes more important as a moulding influence. Prior to eruption of the permanent dentition, increase in size of the arches with spacing of the maxillary temporary incisors occurs; the rounding of the arch depends upon action of the tongue. The growth and advancement of the mandible provide more space for the first permanent molars in both vertical and horizontal planes. Evidence of this change in the mandible is obtained by observing that the temporary incisors show signs of attrition upon their free margins. The mandible and the maxillæ, through the occlusion of the teeth, possess a much more definite relationship, but the small cusps of the temporary molars still allow of great latitude of movement. If the edge-to-edge occlusion of the incisors has not taken place, the limitation of movement is much greater. Locking of the lower incisors behind the upper ones should be regarded as pathological if at all marked, as this is evidence of failure of the mandible to advance.

Permanent dentition.—At approximately the seventh year, by the eruption of the first permanent molars, the relationship of the mandible to the maxillæ is fixed more definitely by the interlocking of the large cusps of these teeth. About one-third of the mandibular molar should be in advance of that of the maxilla. This relationship, and the full eruption of the teeth in the vertical plane is of the utmost

importance, and should take place at this stage, although it cannot yet be regarded as complete.

In the adult the ideal conditions are fulfilled when the teeth are arranged with perfect alignment in rounded arches and with the crowns free from the gum, which is firmly attached to the bone, the thin margin being well protected by the overhanging bulge of the enamel of the tooth. The arch of the alveolar bone should be approximately as large as that of the crowns of the teeth with vertical implantation of their roots.

The oral cavity should be free from air, the tongue should occupy the area inside the dental and alveolar arches, whilst the lips and cheeks should be in close contact with the outer side of the arches.

The oral cavity and its sphincters.—There are two portals to the oral cavity: the lips anteriorly, and the tongue, soft palate and pillars of the fauces posteriorly; these we have called respectively the anterior and posterior sphincters of the oral cavity. The movements of the mandible and of the floor of the mouth provide two further factors, which can cause variation in the form and size of the oral cavity.

By the act of sucking or swallowing the lips are closed, the tongue is brought into contact with the palate and the inner aspects of the dental and alveolar arches, the soft palate is depressed, and the lips and cheeks are brought into contact with the outer aspects of the dental and alveolar arches, whilst the saliva provides the moisture necessary to complete the obliteration of air. The negative pressure produced in this manner constitutes, in our opinion, the most important feature for the development of the normal growing mouth and for prevention of local disease. The maintenance of a negative pressure is dependent upon the action of the tongue. It was realized as important by Metzger and other German workers.

The moulding of the arches by the tongue, as was pointed out by Sim Wallace, is of the greatest significance. The depression of the soft palate and the fixation of the mandible in the normal position aid respiration by opening the airway, whilst the parts suspended from the mandible and the hyoid bone are maintained in a correct position. During inactivity the muscles of mastication by their tone help to support the mandible.

The tension of the lips and cheeks maintains a more healthy condition of the gums than where relaxation occurs. That negative pressure occurs in the mouth can be demonstrated in many ways. Donders used a manometer to show this, and we devised a special apparatus connected with a water manometer; fifty-four cases were tested, those with a negative pressure recorded an average of 10 cm. of water Its use was not always easy on account of the consciousness of the individual tested, but by waiting for a sufficient period of time a fairly accurate reading was obtained. In cases where a negative pressure was absent there was failure of either the anterior or posterior oral sphincter, or of both.

During rest it is usual for the teeth to be just apart, but during swallowing they are brought together. Slight dropping of the mandible, the sphincters remaining closed, will add to the negative pressure and so more firmly hold the soft palate to the tongue and the lips and cheeks to the teeth and jaws. By pulling down the lower lip when the mouth is closed the pull of the negative pressure can be detected and the noise of air entering the mouth can be heard when the lips are forcibly separated.

The pad of tissue which frequently is seen to project from the tongue or cheek into a space resulting from an absent tooth, is further evidence of negative pressure.

The swallowing of food and saliva demands closure of the lips and the creation of a negative pressure in the oral cavity. The amount of saliva secreted daily is from one to two litres. It maintains the moist condition of the mouth and its frequent secretion demands repeated acts of swallowing. The constant

irrigation of the mouth with saliva and the frequent swallowing necessary, aid considerably in keeping the mouth healthy; it certainly assists in the removal of food particles by the action of the tongue, lips and cheeks. The saliva with its mucin must be a valuable lubricant and protection to the teeth and gums, in fact a properly lubricated mouth will hardly allow of actual contact between food and teeth and gums, except on the crushing surfaces of the teeth. The loss of this irrigation of the teeth, which are exposed to the air when the anterior oral sphincter fails, greatly favours pathological changes in the teeth and in their supporting structures.

Conditions associated with failure of the oral sphincters.—In the past it has generally been concluded that because an individual has his lips apart he of necessity breathes through his mouth. That this is not the case has been already pointed out. Certain abnormal and pathological conditions usually described as associated with mouth breathing are, therefore, more correctly enumerated as accompaniments of failure of one or both of the oral sphincters.

External appearance.—The lower part of the face is generally expressionless. A striking change in appearance occurs during animation, as in smiling.

Anteriorly: Nose usually small, with wide bridge, which is but little raised from the face. Prominence of alæ less marked than normal. The orifice is small and tends to be rounded, whilst if the nose is large the orifice is slit-like. The tip may have an upward tend if the nose is small. Central area of face: flat and relatively small. Cheek bones: less prominent than normal. Upper lip: short and everted in certain types. Lower lip: pendulous and thickened. Both lips often dry and cracked. Chin: small, rounded and receding. Neck; frequently a fold beneath the chin (double chin).

Lateral aspect: The face runs into the neck, and there is often a definite bulge below the mandible which appears to be displaced backward. The angle of the mandible is not distinct. The ramus of the jaw appears to be relatively shorter, so that the angle of the jaw is nearer to the zygoma than normal.

Internal conditions.—Nose: usually narrow from side to side, especially above; septum, often deviated, as if bent in the vertical plane. The anterior end is often deflected from the middle line. Turbinals: The mucous membrane is frequently thickened. In the nasopharynx the Eustachian cushions are often approximated.

Adenoids and nasal obstruction.—Contrary to the generally accepted view, we are of opinion that nasal obstruction is rarely caused by adenoids. Too often in the past cases of children with lips apart have been diagnosed as "adenoids" and hurried off to operation; it is not surprising that some adenoids have been found, as adenoid tissue is present in the nasopharynx of most children. It is true that in a few cases the lymphoid tissue of the nasopharynx is so much increased in amount that it blocks the airway. Most of the children, however, who are diagnosed as cases of "adenoids" and benefited by operation have a mass of lymphoid tissue in the nasopharynx of such a size that it could not possibly cause any obstruction. We have been impressed by the fact that in very few of the cases we have seen with open mouth is the airway in any part of the nose or nasopharynx less than that through the open glottis. It is very difficult to see, therefore, how real obstruction could be caused by the adenoids. Moreover, in very many cases the open-mouth habit continues, in spite of the removal of adenoids, unless the child is instructed and trained otherwise. We have made many attempts to estimate the amount of airway through the nose but have so far failed to devise any satisfactory method which is of sufficient accuracy for comparison. In this country the term "adenoid facies" has been used to describe a particular facial appearance in children and adults in which most of the characteristics already defined are pronounced. Such a facial appearance may be present without adenoids, and without any history of their ever having been removed. In our opinion it is an example of the habit of the open mouth which has developed in early life in a particular type of individual.

A good deal has been written recently regarding nature and causation of adenoids. By some they are regarded as part of a general enlargement of all the lymphoid tissue throughout the body, a condition to which the name "exudative diathesis" has been given. By others they are looked upon as Nature's reaction to local sepsis. The committee set up by the Board of Education to inquire into the incidence of and conditions associated with enlarged tonsils and adenoids came to the conclusion that while slight hypertrophy of the pharyngeal tonsil was not associated with other indications of deficiency of vitamin D, marked hypertrophy probably was. They suggest, however, that as a sufficiency of vitamin A is necessary to maintain a healthy condition of the mucous membrane, an insufficient supply of this vitamin might predispose to an overgrowth of lymphoid tissue in the nasopharynx.

Any theory of the ætiology of adenoids must explain the fact that they may be present and give rise to symptoms within a few days of birth, and also the extraordinary improvement in general health which not infrequently follows the removal of a mass which is insufficient in size to cause nasal obstruction.

Adenoids are said to develop frequently after infectious fevers. Infection of the nasopharynx is common in these fevers, and an increase of the lymphoid tissue might be expected to result if adenoids are due to chronic infection. We have not been able, so far, to investigate the condition of the nasopharynx of patients before and after such a fever, so as to ascertain whether the adenoids do really increase in size, or whether the condition observed is due to the development of the open-mouth habit, from muscular weakness or other cause induced by the illness.

Changes in the mouth.—When a careful examination is made of "mouth-breathers," conditions are found to be far less simple than would at first appear, considerable variation depending upon the different forces operating. Presence of a negative pressure in the oral cavity, during periods of rest, is the most important factor in these cases. The negative pressure may be only slight, but when present, well-formed arches are found. If it fails, a sequence of events results with all the changes recognized as due to mouth-breathing.

The most important changes are associated with the position and the action of the tongue. Various deformities can be explained according to the relationship of the tongue to the palate and the dental arches. The loss of negative pressure may be due to failure of the anterior oral sphincter (lips), the posterior oral sphincter (soft palate and tongue), or of both, each resulting in a particular type of deformity.

Before discussing these types, a condition in some degree common to all is best described here.

Failure of mandible to advance.—As was shown by Metzger, with a negative pressure in the oral cavity, the mandible and the soft parts attached are supported by atmospheric pressure, in addition to the tone of the muscles of mastication. When the former fails, the mandible, with the tissues attached, is pulled downwards and backwards as is well seen under an anæsthetic and in the post-mortem subject. The mandible is supported chiefly by muscles attached to the posterior half of the body of the bone. The fulcrum of movement is at the two condyles, the hindmost part of the bone. The hyoid bone is in a plane in front of the coronoid processes, i.e., anterior to the insertion of the powerful muscles of mastication. Muscles from the hyoid are attached to the inner side of the mandible both in front and at the sides. The hyoid gives attachment to muscles from the tongue and from the larynx, so that with absence of negative pressure in the oral cavity the weight of the structures supported by the mandible holds it in a backward position and brings about the post-normal occlusion so frequently present in so-called "mouth-breathers." It also allows the base of the tongue to fall back, thus diminishing the airway. This position has a most important influence upon the molar teeth which are prevented from complete eruption in a vertical direction, as occlusion occurs too soon. In such cases the normal growth is impaired.

That the explanation given is probable can be demonstrated by the use of appliances which correct the position of the mandible and allow of eruption of the molars. Also if orthodontic treatment is undertaken without correction of the imperfect vertical development, failure supervenes. The most disastrous results follow an attempt at correction by extraction of teeth; in fact, the deformity is increased and the results may be appalling.

Failure of oral sphincters—Returning to the failure of the oral sphincters: if the lips are just apart, i.e., failure of the anterior sphincter, and the tongue is in contact with the palate whilst the posterior sphincter is closed, the loss of negative pressure occurs within the lips only. The mandible is usually normal posteriorly but the arches are rounded, the bite is too close and the mandibular incisors impinge on the palate. The maxillary incisors may project, particularly if the lower lip is inside them. Quite frequently they are more or less vertical or even slope inwards. The palate is flat.

When the anterior oral sphincter fails and the tongue is not in contact with the palate, except at the back, the posterior sphincter being closed, there is marked deformity in the anterior part of the mouth. The palate is high.

When the posterior sphincter fails alone, the deformity in the mouth is not so marked, but failure of this sphincter, the anterior being closed, does not admit of negative pressure being maintained in the mouth.

When both sphincters fail, some air passes through the mouth as well as the nose during respiration; there is marked deformity. Absence of the tongue, during rest, against the palate leads to failure in moulding the maxillary arch and there may be deformity of the mandibular arch in those cases where the tongue is raised above the level of the mandibular teeth.

As a result of the action of the tongue it is unusual to find marked deformity in the posterior part of either arch, although the maxillary arch may be narrower than normal whilst the mandibular molars may have an inward inclination.

A careful consideration of the action of the oral sphincters, the tongue, lips, cheeks, and other mechanical forces will provide an explanation of the deformities to be met with.

Tension ridges.—Examination of the teeth and gums will determine in most cases the exact position assumed by the lips, cheeks and tongue when the oral sphincters fail.

The surfaces of the teeth, exposed to the air, fail to be cleansed by constant irrigation with saliva and by friction of the soft parts. A deposit of débris, materia alba, is present even in well-cared-for mouths, and calculus or tartar can always be detected beneath the gingival margin. Also they are frequently stained, particularly at the necks. The level at which the lip lies can be readily detected by observing the area stained.

Where the mucous membrane and gums, particularly the latter, are compressed by the lips, cheek and tongue, they present a smooth, firm surface; where the tissues are not compressed, they become swollen and œdematous. At the junction between the compressed and uncompressed areas a definite ridge can be seen, formerly called by one of us a "lip ridge," but better described as a "tension ridge." The ridge is most readily seen beneath the lip when the anterior sphincter has failed. The gum surface on which the lip rests is smooth and firm, whilst the gum exposed to the air presents a characteristic swollen appearance; the ridge defining the areas is the "tension ridge." Where the lips and cheeks are lax a tension ridge is present along the alveolar margin even to the last molar. The failure of either sphincter will produce such a condition. Similar ridges may be found on the lingual aspect of the arches. Sometimes large masses of thickened muco-periosteum are found around the maxillary molars in individuals who rarely place the tongue upon the back of the hard palate. Failure of the oral sphincters is always present in these cases.

The tension ridge lies frequently in a line along the necks of the incisor teeth, the

swollen part corresponding with the papillæ. This results from either the upper or lower lip being the more retracted.

In those whose sphincters habitually fail, swallowing, with the production of a negative pressure, is followed by relaxation and the entrance of air; atmospheric pressure is not established throughout the whole mouth, the posterior sphincter may still be closed; also air fails to enter the sulci completely. This applies particularly to the sulcus of the upper jaw, where tension of the cheeks and capillary attraction will tend to maintain the moist surfaces above the necks of the teeth in contact. The flow of saliva from the parotid will break the contact but it also demands a further act of swallowing. The slight negative pressure with the tension of the cheeks will act as a constricting force upon the base of the maxillary dental arch. Where the dental arches are well expanded, in those cases in which the lips are apart and the negative pressure is maintained behind the incisors, the inequality between the base and arch is most marked, and the pressure in the sulcus is lowest. A most obvious tension ridge is present. The very marked character of the tension ridge, indicating a considerable contrast between the compressed and uncompressed areas, strongly supports this view. This constricting band will tend to influence nasal development both laterally and anteriorly. Pitkin has shown that the abnormal nose does not swing out so far from the cranium as the normal nose. It would appear to be an important factor in the production of the flattening found in the "adenoid facies."

Causes of failure of the oral sphincters.—(1) The commonest cause appears to be concerned with failure of muscular control. The anterior sphincter is most easily observed and its failure may follow any condition of health which produces muscular weakness. The sister of the maternity ward tells us that when a baby becomes unwell it tends to sleep with its mouth open and on recovering to close it again. In twenty-six out of fifty-two cases of failure of the anterior sphincter which we have carefully investigated, there is a history of a severe illness or operation in infancy. It would seem probable that it was the muscular weakness resulting from this that first initiated the habit. In old age when the musculature is becoming enfeebled the mouth tends to drop open during sleep. In this case, however, the posterior oral sphincter often fails also and mouth-breathing results. During mental concentration the mouth sometimes drops open, presumably as a result of muscular relaxation, but the condition is only temporary. (2) Under conditions demanding a more rapid respiratory interchange, as in pneumonia, oral breathing becomes necessary. It is possible, particularly in children, that the habit thus acquired may persist. (3) Failure of the anterior sphincter (open mouth) often occurs in several members of the same family, parents and children. We are of opinion that imitation is an important factor. It is notorious how children copy the most trivial habits of their parents and those with whom they live. (4) Lowndes Yates regards a faulty position of the neck, in which the head is pressed forward, as a probable cause. He suggests that as a result of the cervical vertebræ being pushed forward and the head extended, there is a definite pull on the mandible.

Possible causes of mouth-breathing.—It has already been shown that the open mouth habit is common, whereas mouth-breathing is comparatively rare. Only if both anterior and posterior sphincters fail is mouth-breathing possible. Usually in such cases the breathing is partly oral and partly nasal, and only if there is definite obstruction in the nose or nasopharynx, or if by muscular action the soft palate is raised and held in contact with the posterior pharyngeal wall, will respiration become completely oral. We have shown, moreover, that in a good many individuals either the anterior or the posterior sphincter is inactive. Therefore, but a single step is necessary—the failure of a second sphincter—to establish oro-nasal breathing.

The mucous membrane of the nose, especially that covering the inferior turbinated bones, contains erectile tissue, This is liable to swell in conditions of catarrh,

and also when the atmosphere is warm and moist. It is suggested that a superabundance of clothing by day, and more especially by night, by interfering with normal perspiration may result in an increased need for loss of fluid from the nose and so swelling of this erectile tissue may result. Lastly, it is known that the prone position often results in increased swelling of the mucous membrane of the nose. We anticipated, therefore, that not a few nose-breathers with lips apart would be found to be oro-nasal breathers at night, but as has already been shown this was not the case.

In those cases of adenoids in which oro-nasal breathing is developed, the sequence of events may be as follows. At the junction of the nasopharynx and nose the direction of the inspiratory and expiratory currents of air are changed. Air on inspiration through the nose will impinge directly upon the pharyngeal wall. Adenoids which have developed in this situation may, therefore, easily become infected, if the inspired air is germ-laden. The spongy structure of the adenoids is such as to make them a receptacle for retaining micro-organisms which have been demonstrated to exist in their recesses. A constant source of supply of micro-organisms having in this way been provided, it is easy to see that attacks of nasal catarrh may be developed, as experience shows to be the case, with intermittent swelling of the mucous membrane of the nose. As a result, oro-nasal breathing may follow, and further hypertrophy of the adenoids may lead to oral breathing.

Effects of nasal obstruction.—The effects of nasal obstruction upon the architecture of the nose and mouth may be to some extent elucidated by a study of the somewhat rare condition of congenital atresia of the post-nasal orifices. When this condition is bilateral it is clear that no air can pass through the nose and that the mouth must be constantly kept open for breathing. Up to the present some 180 cases of congenital choanal atresia have been described and of these about a quarter are bilateral.

Unfortunately, in the literature the unilateral and bilateral cases are not always clearly separated from one another. It would appear, however, that in both types deformity of the chest is rare, but that some amount of arching of the hard palate is usual. Thus Wright describes two such bilateral cases. Richardson quotes Haag as stating that he had collected from the literature records of sixty-eight cases, but that in only twenty-one was there any mention of the form of the hard palate. In fifteen of these the palate was high and in six normal. Richardson goes on to state that John Lang's six cases and Kahler's nine all had high arched palates. Porter, quoted by Fraser, states that in 87·5% of cases the palate was high. It would seem clear, therefore, that on account of the complete nasal obstruction in bilateral cases and partial obstruction in unilateral, the action of the tongue in moulding the palate has been interfered with.

Turning now to deformities of the face and nose, one is surprised to find how few are mentioned, especially in bilateral cases. Thus, Wright states that in his two bilateral cases the nasal passages were wide and the septum straight. Ridout, in another bilateral case, states that radiographs show the frontal sinuses and antra of normal size. Richardson says that there is usually a widening of the nasal chambers and that the facial appearance does not show the changes, which are usually manifested so markedly in other forms of nasal obstruction. This is confirmed by Roth and Geiger, who state that: "Changes in the facial expression are not so marked as in complete nasal obstruction due to vegetation in the nasopharynx and pharynx." Wright sums up the situation by saying: "Apparently pure mouth-breathing produces some degree of narrowing and arching of the palate, but chest deformity, narrowing of the nose, collapse of the alæ, deflection of the septum, and changes in the ears are the result of respiration through a partially obstructed passage, or of infection, or of both," and Tilley confirms this observation.

To sum up then, it would appear that complete congenital nasal obstruction may

be associated with few changes except in the palate, and that these changes have apparently resulted from the absence of moulding by the tongue in consequence of the open mouth.

On the other hand, associated with partial nasal obstruction are not infrequently marked changes in the nose and face. To explain this two theories have been elaborated. The first, associated with the name of John Hilton, suggests that disuse of the nose during growth of the organism will lead to imperfect evolution and expansion of the nasal framework, owing to the physiological stimulus of functional activity being in abeyance. But surely the physiological stimulus will be most completely in abeyance when the nasal obstruction is congenital and complete. The second theory suggests that during normal respiration there is a decreased pressure of air during inspiration and an increased pressure during expiration, and that when the nasopharynx is blocked by adenoids, this rhythmic increase and decrease is lessened. It must be pointed out, however, that in cases of nasal obstruction at the anterior nares, from collapse of the alæ nasi, for instance, the variations of pressure in the nose must be greater than normal and that in posterior choanal obstruction they must be entirely absent, yet in neither condition is there evidence of any contstant deviations from the normal in the structure of the nose. It would seem clear, therefore, that deformities of the nose and face are more often the cause than the result of the nasal obstruction.

With regard to deformities of the chest, the explanation may be different. A child with congenital nasal obstruction, if it survives, quickly gives up the struggle and becomes a mouth-breather. On the other hand, when the obstruction is variable, and incomplete, the physiological urge for nose-breathing is constantly exerting itself and retraction of the sternum and lower ribs may result.

Conclusions.

(1) The urge for respiration through the nose is so great that mouth-breathing is established with difficulty.

(2) Oro-nasal breathing is uncommon. Oral breathing is rare.

(3) A negative pressure is normally present in the oral cavity during inactivity.

(4) Failure of one or both oral sphincters results in loss of negative pressure.

(5) The loss of the normal negative pressure in the mouth is associated with impaired action of the tongue, lips, cheeks and other moulding forces of the jaws. The deformities of the jaws result from the impaired and misdirected action of those forces.

(6) Failure of the anterior oral sphincter is common but does not indicate mouth-breathing.

(7) Failure of the posterior sphincter results in absence of fixation of the soft palate to the tongue with impairment of the airway.

(8) Backward position of the mandible results from failure of either oral sphincter; it is most marked when both fail. The associated falling back of the tongue impairs the freedom of the airway.

(9) Tension ridges upon the gums and mucous membranes mark off the areas where compression of the tissues exists from where it is absent.

(10) Nasal obstruction by adenoids rarely occurs, although the associated catarrh and swelling of the erectile tissue may diminish the airway.

(11) Deformities in the nose may cause obstruction but are not caused by it.

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Mr. T. B. Layton said that in a discussion such as this it was necessary to distinguish between: (1) the so-called typical adenoid facies; (2) the high-arched palate of the rhinologist, and (3) the contracted arch with dental irregularity of the odontologist. As to the typical adenoid facies, it was a myth for which no evidence had ever been brought forward, and he felt that it had received its quietus that night. He thought that it was a remarkable phase in the history of medicine that this hypothesis, the origin of which it was impossible to trace, had been accepted as a fact by practically the whole medical profession in the country. It was to the credit of the dental profession that they had approached the subject with an open mind and found that the whole of what they had been taught by surgeons of other departments was wrong. It was, he believed, Mr. Rollinson Whitaker[1] who had first begun to doubt the accepted teaching of rhinologists that obstruction due to an excess of lymphoid tissue in the nasopharynx by preventing nasal respiration was the cause of a particular configuration of the face. During the past ten years he had found his younger dental friends becoming more and more confident in the fallacy of that teaching, while his junior medical and surgical colleagues still brought him patients with that type of countenance under the assumption that it was a definite indication of the necessity to scrape the nasopharynx.

He (the speaker) feared that the readers of the paper might be trying to make the pendulum swing too far. It was difficult to change the ideas that one had held for a quarter of a century, in a day, and to accept the practical non-existence of

[1] *Brit. Dent. Journ.*, 1911, xxxii, 537.

mouth-breathing in children was difficult. He thought that it would be necessary carefully to watch people and to see if the observations of the readers of the paper would be confirmed.

The paper afforded good evidence of what a bad term was the word *adenoids*. This vague term was one which everyone who used it assumed would be understood by his listeners; yet it was difficult to define. In this paper it was used in one place to denote a normal structure where "lymphoid tissue" was meant; in other places the word was put between inverted commas, showing that the authors did not accept the meaning given to it by others; while in the only place where mention was made of what he (Mr. Layton) would accept as adenoids the condition was thus described: "the lymphoid tissue of the nasopharynx is so much increased in amount that it blocks the airway." It was interesting to note that this was described as being rare, thus supporting his own teaching during the past few years that rhinological adenoids was a disappearing condition and that the operation for it was seldom needed at the present day and would ultimately follow the amputation of the uvula or the removal of the inferior turbinal into the limbo of forgotten industries.

In his recent book, "The Scientific Outlook" (p. 63), Bertrand Russell had said, "Throughout the history of physics the importance of the 'significant' fact has been very evident." He (the speaker) thought this principle should be applied to clinical medicine and made the "significant" case, a form of study which has been somewhat neglected of late. He proposed to show illustrations of cases significant to the matter under consideration.

Case I (*Trans. Brit. Soc. Study Orthodont.*, 1914, p. 40, fig. 1) was that of a youth, aged 21, with the facies in question. He had the high-arched palate to a marked degree but there was no sign of contraction of the arch and no irregularity of the teeth. This showed that the high-arched palate of the rhinologist and the contracted palate of the odontologist were not the same, and that the latter was not necessarily connected with the so-called adenoid facies.

Cases II and III were the two sisters with congenital stenosis of the posterior choanæ described by Mr. Wright, to which reference had been made in the paper. Mr. Wright stated that these girls did not have the adenoid facies, yet the casts of their mouths—of which he had allowed the speaker to have copies made—showed the high-arched palate and an irregularity of the teeth, although this was not the irregularity usually present with the contracted arch.

These cases showed that it was possible to have the high-arched palate without the so-called typical adenoid facies, and that even if the former might be caused by mouth-breathing the latter was not.

Cases IV and V were two children (*Ibid.*, 1914, p. 40, fig. 2), in whom the respiration as judged by the criteria of those days was identical, yet one had marked contraction of the arch with a high palate and the other had a palate and a row of teeth that might be taken by anyone who wished "to conceive an ideal normal," a hypothesis that he, the speaker, would not accept.

Case VI (*Ibid.*, 1914, Case D II) was a girl, aged 12, who had apparently been a mouth-breather from birth. Yet she had a palate that might have served for Trilby's as described by Svengali (p. 71).

Mr. A. R. Friel said that a common feature of nasal obstruction was congestion of the nose in sufficient degree to cause mouth-breathing in certain cases. He described various mechanical lip-exercising devices for inducing closure of the mouth.

Mr. E. D. D. Davis urged closer co-operation between the laryngologist and the odontologist. The mouth-breather, often found with a clear nose, was usually of inferior physique, as compared with the nose-breather; he more easily caught cold and acted as a carrier of infection.

Mr. J. G. Turner considered adenoids to be a local disease. A large number of children, otherwise well grown, yet suffered from all the disabilities that adenoids could produce.

Dr. R. P. Garrow explained that every educational authority in the country was bound to provide a scheme for the removal of tonsils and adenoids, but the more he had seen of those operations in school children the less he had liked them. He suggested that a great service would be done if copies of the paper were sent to every school medical officer.

Mr. Harold Chapman asked if models of children's mouths had been taken in very early years, and if any change in the shape or size of the dental arches had been observed. In many cases patients were forced to keep their mouths open owing to the position of the teeth.

Mr. Somerville Hastings, in reply, said that very few children breathed through their mouth, though many kept their mouth open. What had been called adenoid facies was a condition in which the mouth was open but not necessarily used for breathing. He also had seen the casts of the mouths of Mr. Wright's cases referred to by Mr. Layton (Cases II and III). He was in Bristol a few days ago and Mr. Wright had shown him also casts from the mouths of the same girls taken two years after the obstruction had been relieved by operation. As the result of two years of closed lips, the jaws and palates had become almost normal. He disagreed that adenoids practically never caused nasal obstruction, having seen cases in which the nose was completely blocked, though such instances were rare. When adenoid tissue became infected it might act as a septic focus and cause nasal obstruction and give rise to trouble in other ways.

Mr. Warwick James explained that there were many aspects of the subject, but the paper had dealt mainly with local changes. Lip exercisers were of value chiefly as a daily reminder that the lips must be closed and a negative pressure produced by swallowing; on this account they should be used in the early morning. Orthodontic treatment should be commenced at as young an age as possible.